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Salmonellosis at The Mount Sinai Hospital: A Ten Year Survey (1953-1963)

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The extensive distribution of *Salmonella* microorganisms in nature affords many opportunities for the infection of humans. Meat from cattle, pigs, chickens, turkeys, and ducks; fish and shellfish; milk and eggs may be contaminated and be responsible for cases of Salmonellosis when ingested. An indefinite proportion of the general population are carriers of the organisms, are often symptomless, and represent an infectious hazard to less immune individuals, especially when as carriers they are involved in the preparation, handling and dispensing of food or food products. Water and food, when contaminated by the droppings of dogs, cats, rats, mice and flies which may contain *Salmonella*, may further be a source of contagion.

Salmonella infection is manifested clinically in four forms: 1) gastroenteritis, with or without fever, 2) septicemia, 3) focal infections, as for example, osteomyelitis and aortitis, and 4) the carrier state. All of the more than four hundred described *Salmonella* serotypes are potentially capable of producing these protean manifestations, but certain serotypes are more likely to be associated with the last three forms, as will be shown in the following report.

The diagnosis of Salmonellosis is primarily dependent upon the isolation and identification of the etiological organism based upon its possession of certain morphological, biochemical and serological properties. These organisms are gram negative, usually motile, noncapsulated, rodlike bacilli particularly characterized by their inability to ferment lactose. Acid and gas are produced with glucose, mannitol, maltose and sorbitol. Hydrogen sulfide production is variable. The methyl red test is positive, ammonium citrate is usually utilized and nitrates are produced from nitrites. Gelatin is not liquefied, indole and acetylmethylcarbinol are not produced, urea is not hydrolyzed, and potassium cyanide sensitivity is negative. Tentative identification based upon the above is confirmed by the agglutinability of the strain under test with one of the various *Salmonella* group antisera.*

The exact incidence of Salmonellosis is unknown. Diarrhea, which is the prime symptom of the gastroenteritis form, is a common, often self-limited occurrence. Only in those cases where cultures are performed can the precise diagnosis be established. In practice the number of requests for this laboratory procedure is

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* The *Salmonella* identity and serotype of all strains included in this survey were kindly verified by the New York *Salmonella* Center at Beth Israel Hospital, New York, N. Y.

highly variable, depending to a large degree upon the suspicion of the clinician. Recent reports indicate an increased incidence of *Salmonella* infections other than those caused by *S. typhosa*, but other factors may be responsible for this apparent rise (1 to 3). These include the development of refinements in laboratory methodology resulting in a greater number of positive identifications as well as an increased awareness on the part of the clinician as to possible *Salmonella* etiology, to the effect that more cultures may be requested. More complete reporting of cases may also have been contributory.

During the ten-year period, from midyear 1953 to midyear 1963, 240 *Salmonella* isolates were obtained in the Bacteriology Laboratory of The Mount Sinai Hospital from 229 patients. A number of strains of the same serotype were recovered from more than one site in the same patient, *e.g.*, stool, blood, and urine. Pertinent data derived from the involved patients were analyzed and the findings in this regard form the basis for the present report.

Identity of the *Salmonella* serotypes cultured as well as the sites from which they were recovered are tabulated in Table I.

Considering the serotypes, *S. typhimurium* accounted for the greatest number, 69 or 29.8% of the total. *S. typhosa* was recovered from 19 patients from 25 body sites. Nine of the ten *S. derby* strains were isolated within a three months' period early in 1963 at which time a number of hospital outbreaks involving this strain were prevalent throughout the Middle Atlantic States. The number and distribution of the remaining serotypes isolated are indicated in the table. Three strains were classified as "*Salmonella*, non-typable," since they possessed the characteristic morphological and biochemical properties of *Salmonella*, but their roughness, resulting in spontaneous agglutination, precluded the possibility of their being grouped or typed by *Salmonella* antisera. Most strains were recovered from the stool (70%) but a significant number were isolated from the blood (16.3%). The remainder, as may be noted, were cultured from a variety of sources.

Definitive conclusions as to increased or decreased incidence of *Salmonellosis* at The Mount Sinai Hospital could not be reached by comparing the total number of isolates obtained in the first and second half of the ten-year study period. One hundred and seven stool isolates were achieved during the first period, 133 in the second; but, considering positive blood cultures, 23 versus 16 respectively were obtained during the same intervals.

Because of the prevailing general impression that *Salmonellosis* is associated with poor sanitation, consideration was given to the socio-economic status of each patient. Findings in this regard are listed in Table II.

The status of 5 patients could not be determined. Eighty-four were classified in the higher category (private, semi-private and private patients of outside physicians) as compared to 116 from the wards, Out-patient Department and Reception. Five positive cultures were obtained from hospital employees, some of whom worked in the Dietary Department. Sixteen strains were cultured from nurses and 2 from house staff physicians. All these strains were recovered from stool culture, ordered mainly for gastroenteritis associated with diarrhea.

TABLE 1

*Salmonella Serotypes Cultured at The Mount Sinai Hospital During Past 10 Years
and Body Sites from Which They Were Isolated*

Salmonella Type	Total Number	Sites of Isolation			
		Stool	Blood	Urine	Miscellaneous
Albany	1	1			
Anatum	5	4	1		
Bareilly	6	4	1		
Blockley	5	4	1	1	
Braenderup	2	2			
Choleraesuis	8	1	4	1	abdominal wall ab- scess 1 chest wall fluid 1
Derby	10	10			
Enteriditis	11	9		1	rectal swab 1
Heidelberg	13	9	3		lung culture 1
Infantis	5	4		1	
Lenta	1	1			
Litchfield	2	2			
Minnesota	1				wound 1
Montevideo	8	7	1		
Muenchen-Oregon	2	1			rectal swab 1
New Brunswick	1	1			
Newington	5	3		1	wound 1
Newport	18	17	1		
Norwich	1	1			
Oranienburg	8	3	4		gall bladder aspirate 1
Panama	1	1			
Paratyphi A	3	3			
San Diego	3	2			vagina 1
Saint Paul	3	2			wound 1
Senftenberg	4	4			
Taksony	9	9			
Tennessee	1	1			
Thomasville	1	1			
Thompson	5	4	1		
Typhimurium	69	48	14	2	thoracic fluid 1 rectal swab 3 abscess 1 bone 3 gall bladder stone 1 gall bladder aspirate 1 bile culture 1 duodenal drainage 1 peritoneal fluid 1 wound 1
Typhosa	25	7	8	1	
Non-typable	3	2		1	
Totals	240	168	39	9	24

Serotypes isolated from the nurses were *S. taksony*, 5, *S. montevidео*, 3, *S. typhimurium*, 2, and one each of *S. anatum*, *S. heidelberg*, *S. senftenberg*, *S. tennessee*, *S. thomasi* and *S. derby*, and from the house physicians one each of *S. newport* and *S. newington*. The relatively high incidence of positive *Salmonella* isolates among nurses may indicate greater risk on their part as a consequence of close exposure to overt or covert cases; however, their own usually closely supervised medical care might have resulted in more cultures being ordered in the presence of symptoms, so that more positive diagnoses were made. One patient, from whom a *S. typhosa* strain was recovered, was a technician in the Bacteriology Laboratory who had worked upon specimens from a patient in the hospital with typhoid fever and later contracted the disease.

TABLE II
Socio-economic Status of 229 Patients with Salmonella Infections

Status	Number	Per cent of Total
Ward, OPD and Reception	116	50.7
Private, Semi-private and Private Out-patient	84	36.6
Hospital Employee	5	2.2
Nurse	16	7.0
House Physician	2	0.9
Laboratory Technician	1	0.4
Unknown	5	2.2
Total	229	100.0

SALMONELLA SEPTICEMIA

Thirty-nine of the *Salmonella* strains were derived from the blood in 39 patients. During their hospitalization, more extensive case histories were available, thereby providing more detailed data for analysis. Considering the types of *Salmonella* isolated from the blood, *S. typhimurium* was obtained 14 times, *S. typhosa* 8 times, *S. choleraesuis* and *S. oranienburg* 4 times each, *S. heidelberg* 3 times and a number of other types, one each (Table I).

The vital statistics of these patients are contained in Table III. As may be observed in the table, the age distribution was broad, as were the other factors listed, but a distinct majority were white males of the lower economic class.

Although *Salmonella* septicemia may occur in previously healthy people, as for example, in acute typhoid fever, it is well known to be associated with other disease entities. Other predisposing or associated diseases, often of a serious nature, were present in a fair proportion of the patients in this series as may be noted in Table IV.

Thus, while no other recorded illness was present in 24 patients, 15 did suffer from a variety of disease states. The concomitant existence of severe hematological disorders in a number of the patients is particularly noteworthy.

The involved patients presented a variety of symptoms and signs (Table V).

TABLE III
Vital Statistics of 39 Patients with Salmonella Septicemia

		Number	Per cent of Total
Age	up to 1 year	7	18.0
	13 mos-5 yrs	7	18.0
	6-10 yrs	5	12.8
	11-19 yrs	3	7.7
	20-49 yrs	8	20.5
	over 50 yrs	9	23.0
Sex	male	24	61.5
	female	15	38.5
Race	white	24	61.5
	Puerto Rican	8	20.5
	colored	7	18.0
Socio-economic Status	ward	23	59.0
	semi-private pavilion	11	28.2
	private pavilion	5	12.8

TABLE IV
Predisposing or Associated Diseases of Salmonella Septicemia Patients

No predisposing or associated disease—24
Biliary cirrhosis and giant cell hepatitis
Acute lymphatic leukemia
Heroin addiction
Cooley's anemia
Post-gastroenterostomy and vagotomy for peptic ulcer—5 years
Post-gastrectomy for peptic ulcer 5 years and post-cholecystectomy 2 years
Congenital subluxation of hip
Chronic myelogenous leukemia
Acute purulent otitis media—2 weeks
Leukemia and Gaucher's disease
Carcinomatosis
Chronic myelocytic leukemia
Hodgkin's disease
Chronic anemia and splenomegaly
Mental retardation and endocrine disorder

Fever, usually high, was the most prominent symptom, although four patients failed to demonstrate any elevation in temperature throughout the course of their infection. Gastroenteritis, manifested by diarrhea, was present in 13 only. None of the symptoms or signs listed are exclusively pathognomonic, for *Salmonella* septicemia and its diagnosis was established almost invariably through a

positive blood culture ordered because of sudden elevation in temperature, or because of persistent fever.

A large number of the blood-derived *Salmonella* strains were tested in the lab-

TABLE V
Presenting Signs or Symptoms in Histories of Salmonella Septicemia Patients

Fever	35
Diarrhea	13
Chills or chilly feelings	10
Bloody stools	8
Vomiting	7
Abdominal pain or distress	6
Nausea	4
Anorexia	4
Malaise	4
Headache	4
Roseola	3
Hematemesis	2
Mental disturbances or disorientation	2
Weight loss	2
Dizziness	2
Slight icterus	2
Constipation	1
Darkly colored urine	1
Herpes labialis	1
Calf pain	1
Pain in hip	1
Pain in knee	1

TABLE VI
Antibiotic Susceptibility of Salmonella Strains Isolated from the Blood

Antibiotic	Number of Strains Tested	Antibiotic Susceptibility		
		Sensitive	Moderately Resistant	Resistant
Chloramphenicol	28	28		
Tetracycline	24	18	2	4
Streptomycin	18	10	3	5
Neomycin	11	11		
Nitrofurantoin (Furadantin)	8	8		
Furazolidone (Furoxone)	5	5		
Polymyxin	6	5	1	
Colimycin	2	2		
Sulfonamide	3	1	1	1

oratory for their susceptibility to a variety of antimicrobial agents; the results of these assays are summarized in Table VI.

All the strains tested were sensitive to chloramphenicol, neomycin, nitrofurantoin (Furadantin) and furazolidone (Furoxone). A high degree of suscepti-

bility to tetracycline and polymyxin was present among them but only 10 of the 18 strains tested were found to be sensitive to streptomycin. Too few strains were tested against colimycin and sulfonamides, so that significant conclusions as to the anti-Salmonella activity of these compounds could not be obtained.

Serum agglutinin titers against stock *Salmonella* strains or against the organism isolated from the patient were determined in 22 of these cases. Titers of 1:160 or higher were observed with 9 only. Some failed to demonstrate any antibody titer. These negative or low titers may well have been the result of early treatment resulting in the rapid elimination of bacterial antigen capable of eliciting agglutinin production. In some of the patients, the possible existence of immunological defects as a result of associated disease that rendered them incapable of reacting to antigenic stimulation must also be considered. Finally, a large number of the sera were drawn and sent to the laboratory for test within 2 to 5 days after the onset of fever, much too early for diagnostic antibodies to be produced.

TABLE VII
Complications Observed with 39 Salmonella Septicemia Patients

None	23	
Death	7	
Persistent stool carrier state	5	(3 <i>S. oranienburg</i> , 1 <i>S. anatum</i> and 1 <i>S. typhimurium</i>)
*Destructive spine lesion—2 mos after acute episode	1	
*Mycotic aneurysm of popliteal artery	1	
*Ruptured dissecting aortic aneurysm—4 yrs after acute episode	1	
*Parotid abscess—2 weeks after acute episode	1	

* *Salmonella* etiology not established.

The complications observed in patients with positive *Salmonella* blood cultures are enumerated in Table VII.

Despite vigorous, intensive treatment, there were seven deaths in this series, a gross mortality rate of 17.9%. A number of these deaths could be attributed to the *Salmonella* septicemia per se (Table VIII, cases 2 and 3 and perhaps case 1), but the demise in the others can with justification be ascribed to the severe associated disease, even though the septicemia may have played a terminal, last-straw role. *S. typhimurium* was involved in five of the seven deaths. Some of the patients were on corticosteroid therapy for their primary disease which may have resulted in the terminal dissemination of a latent local focus. Five patients, despite treatment with a number of different antibiotics to which their organisms were found to be sensitive *in vitro*, were persistent stool carriers at the time of discharge, even though their blood cultures were negative and they were symptomless. Evidence of focal lesions was manifest in four patients, including one with possible osteomyelitis and two with aneurysms. These are known to occur occasionally among patients with systemic Salmonellosis. However, the specific bacteriological identification of the organisms responsible

TABLE VIII
Résumé of Fatal Cases of Salmonella Septicemia

Case	Age	Color	Sex	Salmonella Type	Isolation Sites	Associated Disease	Treatment	Maximum Agglutinin Titer of Blood	Remarks
1	23 mos	W	F	Typhimurium	blood	biliary cirrhosis, giant cell hepatitis	chloramphenicol, neomycin	1:1600	Expired 6 days after onset of acute febrile episode. PM: Liver abscess with positive culture.
2	72	W	M	Oranienburg	blood	post-gastroenterotomy and vagotomy—5 yrs	chloramphenicol, streptomycin, nitrofurantoin, tetracycline	—	Acute onset. Expired within 3 days. PM: Septic splenitis. Positive spleen and heart blood cultures.
3	newborn	W	M	Newport	blood, stool, nose and throat	—	chloramphenicol	—	Diarrhea and fever 1 day postpartum. Expired 3 days. Mother positive stool carrier.
4	64	PR	M	Typhimurium	blood	myelogenous leukemia	chloramphenicol, transfusions, corticosteroids	—	Acute onset while being treated for leukemia. Expired 8 days.
5	63	W	M	Typhimurium	blood, stool	monocytic leukemia, Gaucher's disease	penicillin chloramphenicol, corticosteroids	1:1280	Responded to treatment with negative blood cultures. Developed severe parotid abscess 2 weeks later and expired.
6	56	W	M	Typhimurium	blood	carcinomatosis	chloramphenicol, nitrogen mustard, transfusions, corticosteroids	1:40	Sudden spike in temp. while being treated for severe GI bleeding. Persistent positive blood cultures until expiration 3 weeks later.
7	43	W	F	Typhimurium	blood	chronic myelocytic leukemia	chloramphenicol, mystecillin	—	Sudden onset of T 107°. Expired 5 days.

for the lesions in these patients was not ascertained, so that their *Salmonella* etiology remains speculative.

ACKNOWLEDGMENT

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Sequence of Recovery from Multiple Manifestations of Folic Acid Deficiency

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When patients with marked folic acid deficiency are treated with folic acid, it has been generally accepted that the initial effect is manifest on red cell precursors. The change from a megaloblastic bone marrow to normoblastic erythropoiesis with subsequent reticulocytosis and eventual normalization of the hemoglobin has been emphasized. On the other hand, rapid increase in the platelets and white blood cells prior to the maximum reticulocyte peak has been observed in two patients with megaloblastic anemia of pregnancy treated with conventional doses of folic acid. The folic acid effect on hematopoiesis initially observed in the myeloid cells and megakaryocytes, thus, may be indicative of the different metabolic activity manifested by these specific marrow cells.

To test this hypothesis a patient with multiple manifestations of pure folic acid deficiency was treated with oral microdoses of folic acid and her course carefully followed.

METHODS

Complete blood counts were performed by standard methods every two or three days, while reticulocyte counts and red cell indices were determined more frequently. Reticulocytes were counted using the dry method with brilliant cresyl blue. Serum folic acid activity (SFAA) and vitamin B₁₂ activity were determined microbiologically using *Lactobacillus casei* (1) and *Euglena gracilis* (2) respectively as the assay organism. Serum iron and total iron binding capacity (TIBC) were measured by a modified Ramsay technique (3) and by the Ventura technique (4) respectively. Serum haptoglobin level was determined by the methemoglobin method (5).

CASE REPORT

A 33 year old Puerto Rican female was admitted to The Mount Sinai Hospital for the first time on March 3, 1962. Her diet consisted mainly of bread, pinto beans, polished rice, cheese and, on occasion pork meat. She had had four pregnancies; normal children were born in 1956, 1958, 1960 and on January 11, 1962. All these children were breast fed. During the pregnancies she never visited a prenatal clinic. At the time of the last delivery, the hemoglobin was 6.1 Gm% and she complained of easy fatigability, headaches and dizziness. During the two weeks prior to admission her mouth became sore, there was dysphagia,

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daily emesis and a few loose bowel movements each day. She had lost twelve pounds in weight in three weeks.

Physical examination showed a pale woman who was depressed, forgetful and sullen. The tongue was smooth with poorly papillated edges. The heart was of normal size and there was a precordial systolic murmur. The liver and spleen were enlarged to 4 cm below the costal margins. The skin was normal. The nails were brittle. Neurologic examination revealed no abnormalities. Several large

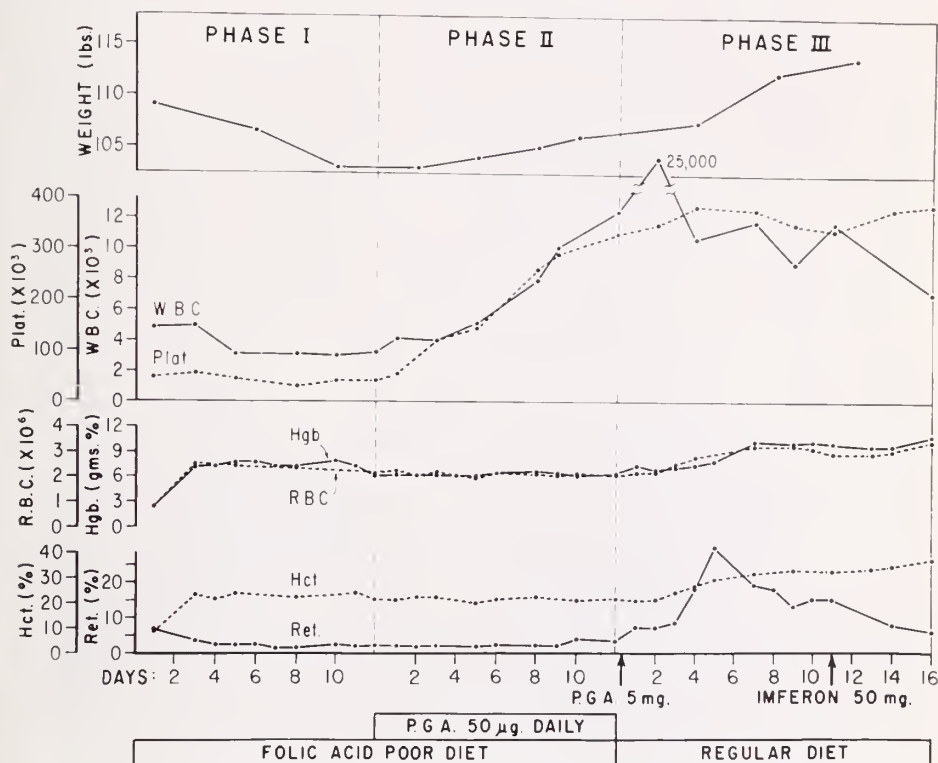


Fig. 1. Changes in peripheral blood and weight correlated with treatment.

hemorrhages were noted in both eye grounds. The electrocardiogram showed diffuse ischemic changes.

The peripheral blood examination revealed the red blood cell count to be 860,000/mm³, hemoglobin 2.6 Gm%, hematocrit 8.5% (Fig. 1). The WBC was 4,950/mm³ with 60% neutrophils, 35% lymphocytes, 1% eosinophils, 2% metamyelocytes and 2% myelocytes. The platelet count was 49,000/mm³ and the reticulocytes were 7.8% (67,000/mm³). Thirteen normoblasts per 100 WBC were present. Macrocytosis, macro-ovalocytes, fragmented red cells and hypersegmented neutrophils were seen on the smears. A sternal marrow aspiration showed megaloblastic erythroid hyperplasia with large metamyelocytes and a myeloid-erythroid ratio of 1.67:1 (Fig. 2A). Alkali resistant hemoglobin was 1.8% and hemoglobin electrophoresis showed only A hemoglobin. Free acid was

present in the gastric juice only after maximum histamine stimulation. Tests for malabsorption including xylose tolerance, vitamin A tolerance, blood carotene level and 72-hour fecal fat excretion were all within normal limits. As shown in Table I, the SFAA and haptoglobin levels were very low, while the serum vitamin B₁₂ level was above the lower limit of normal. The serum iron and TIBC were elevated. Urinalysis was normal and the stool was negative for occult blood, ova and parasites. The blood urea nitrogen, sugar, bilirubin, SGOT, alkaline phosphatase, cephalin flocculation, serum albumin and globulin were all normal.

The patient was considered to have pure folic acid deficiency and the course of treatment was divided into three phases.

Phase I: On admission the patient was placed on a 2500 calorie diet consisting of folic acid-free casein and high dextrin-carbohydrate: rice boiled three times, white meat of chicken, jello, black coffee and water. This diet, similar to the one used by Herbert, contains about 5 μ g of folic acid (6). On the first day she

TABLE I
Changes in SFAA, B₁₂, Iron, TIBC and Haptoglobin

Date	SFAA μ g/ml (7-25)	Serum Vit. B ₁₂ μ g/ml (200-900)	Serum Iron μ g% (75-150)	TIBC μ g% (300-450)	Haptoglobin mg% (75-175)
3/3	1.0	225	203	520	15
3/15	2.1	288	223	490	14
3/26	1.9	244	183	480	12
3/27	24.0	208	—	—	—
4/2	—	—	146	486	—
4/6	7.1	200	50	477	22
4/11	4.1	120	—	—	12
5/15	12.4	328	72	407	200

received a transfusion with two units of packed red cells to alleviate the cardiac stress. Ascorbic acid and the other B vitamins were given daily. After a control period of twelve days, the hemoglobin had dropped 1.9 Gm%, thrombocytopenia had not changed and there was a more severe neutropenia. The percentage of reticulocytes had leveled off to 2.2% (49,400/mm³) and the bone marrow was markedly megaloblastic (Fig. 2B). The patient continued to lose weight, and to have diarrhea and vomiting. The eye grounds now revealed exudates in addition to the hemorrhages.

Phase II: After the twelfth day, 50 μ g of P.G.A. (synthetic folic acid) were added daily by mouth without the knowledge of the patient while she was maintained on the same low folic acid diet. Changes were noted almost immediately and consisted initially of a marked change in the mental pattern. Within six hours the patient felt much better and conversed readily. The weight loss was checked and she gained three pounds in twelve days. The soreness of the mouth disappeared on the second day and papillation of the tongue was normal by the tenth day.

Platelet rise was prompt and the count normal on the fourth day. On the seventh day the WBC was normal and subsequently rose to higher than normal

levels. During twelve days of oral folic acid administration, no effective reticulocytosis was noted and the hemoglobin and hematocrit remained the same. The bone marrow was still megaloblastic (Fig. 2C). The SFAA was 1.9 μg on the twelfth day. The second phase ended when, in the afternoon of that day, the patient had a convulsive seizure. Immediately afterwards the serum calcium, phosphorus, potassium and glucose were at normal levels. On careful examination no focal neurologic abnormality could be found.

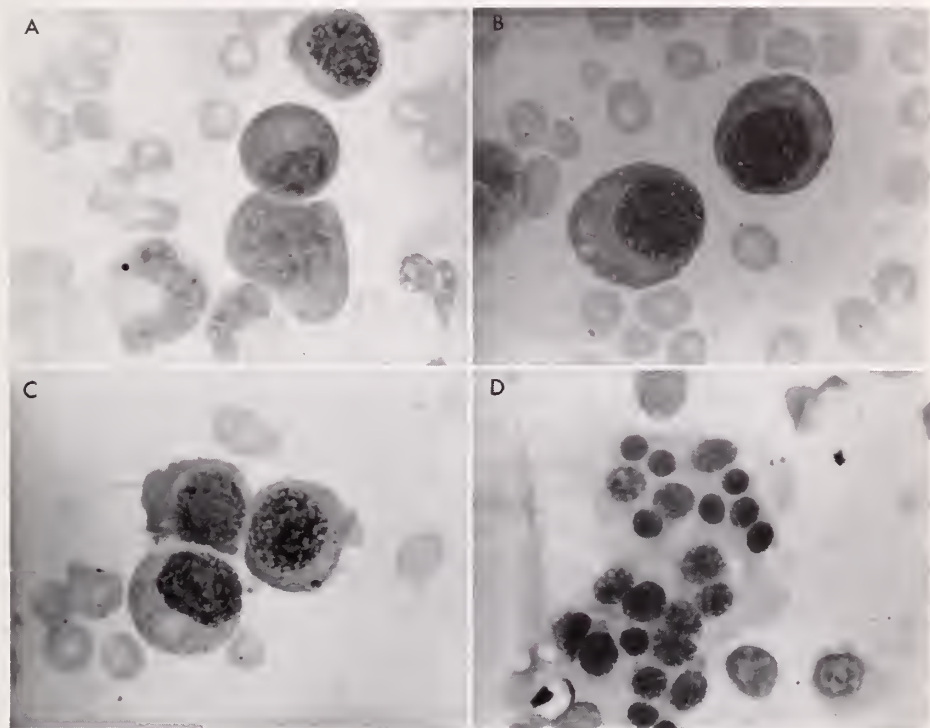


FIG. 2. Bone marrow films. (A) Day 1 of Phase I. Megaloblasts and large metamyelocyte. (B) Day 12 of Phase I. Marked megaloblastosis. (C) Day 12 of Phase II. Megaloblastic changes still present. (D) Day 45 of Phase III. Nest of normal erythropoiesis.

Phase III: After blood was obtained for determination of SFAA, serum iron and vitamin B₁₂, 5 mg of P.G.A. was given by mouth and a normal diet started. There was an immediate rise of the reticulocyte count which was sustained at about 7% for three days. During those days the white cells doubled in number and fell to a normal level on the fourth day, at which time the reticulocytosis became more evident and reached a maximum of 30% (891,000/mm³) on the fifth day. This was followed by a rise of the hemoglobin, hematocrit and red cells. On day 11, the serum iron had dropped to 50 gamma% and the patient was given 50 mg of iron intramuscularly. In Phase III the patient gained seven and one-half pounds while in the hospital. She was discharged and advised to eat fresh folic-acid rich food. She returned one month later with a normal blood count and marrow (Fig. 2D). The serum iron was still low, while the serum vitamin B₁₂

level, which had dropped to 120 μg per ml, was now 328. The liver and spleen were no longer palpable and the heart murmur had disappeared.

COMMENTS

Three factors contributed to the development of the folic acid deficient state in this patient: 1) poor diet, 2) repeated pregnancies and 3) breast feeding. The principal factor no doubt, is the poor diet with the additive vitamin demands of the growing fetus leading to a rapid development of the deficiency state (7). Lactation leukopenia has been known to occur in rats fed a purified diet to which sulfasuxidine was added; this could be effectively prevented by P.G.A. administration (8).

Most of the manifestations of severe folic acid deficiency, including the pancytopenia, weight loss, vomiting, diarrhea, soreness of the mouth, smoothness of the tongue, the retinal hemorrhages and enlargement of liver and spleen have been described in man and in animals placed on a folic acid free diet (9 to 11). In addition, our patient was depressed, forgetful and sullen. The convulsive seizure which occurred while the patient was still folic acid deficient may be of significance. Zalusky and Herbert reported a syncopal episode in their patient (12). It is of interest that treatment with folic acid can reduce the number of fits in epileptics with anemia (13). The anemia in these patients is macrocytic and caused by folic acid deficiency secondary to anticonvulsant drugs.

Rather than use the conventionally large dose of folic acid which could mask the sequence of recovery, a microdose of 50 μg was used. Recently Sheehy, *et al.* reported hematologic improvement in patients with tropical sprue by adding 25 to 50 μg of folic acid to the normally poor diet of their patients (14). Zalusky and Herbert obtained response with 50 μg a day intramuscularly in a scorbutic patient with folic acid deficiency (12). Their patient was maintained on a folic-acid-free diet supplemented with ascorbic acid and the other B vitamins. The most immediate effect of folic acid in our patient was the change in personality within six hours after the first microdose. This change is similar to that observed by Herbert (6). The cessation of weight loss and the subsequent weight gain while in Phase II can be attributed solely to the addition of folic acid to the diet. There was a small, noneffective rise of the reticulocyte count during a period while the platelet and white cell count returned to normal levels. No changes of the hemoglobin and hematocrit occurred during Phase II and the serum iron did not change significantly. A rise of the WBC and no increase of the hemoglobin as found here has only been reported in animals (15). Mention has been made that the platelet count may begin to rise prior to the maximal reticulocyte response in some patients with pernicious anemia when treated with vitamin B₁₂ (16). The rapid rise of the platelet and white blood cell count had previously been observed in two of our patients with megaloblastic anemia of pregnancy. In the first patient, one day after receiving 30 mg of P.G.A. intramuscularly, the platelet count rose from 16,000 mm^3 to 56,000 mm^3 , while the WBC rose from a pretreatment level of 1,200 to a normal level prior to the reticulocyte peak. In the second patient, the platelet count rose from a level of 94,000 to 598,000 and

the WBC from 4,100 to 7,400 in two days. Maximum reticulocyte response occurred on the sixth day. Sawitsky has observed similar rapid increase of platelets and WBC before a rise in reticulocytes when folic was given to a patient with severe megaloblastic anemia during the puerperium (SFAA was 1.4 $\mu\text{g}/\text{ml}$) (17).

Indirect confirmation of this preferential uptake of folic acid by platelets and white cells over red cells, has been found by Herbert (6). After a long period of folic acid depletion, he noticed a drop of the red blood cell count and percentage of reticulocytes, whereas the platelets and white cells remained at normal levels. In Phase III, the serum iron level fell as expected (18). The fall in the serum vitamin B₁₂ level was significant. This interrelation of folic acid and vitamin B₁₂ has been observed previously (19). Although the serum bilirubin level was normal throughout this study, the low haptoglobin values indicated increased breakdown of hemoglobin-containing cells (20).

It is possible that 50 μg of folic acid orally per day might have been sufficient to cause a complete hematologic response in our patient if given over a prolonged period of time; it could be an adequate dose to prevent dietary deficiency of folic acid. However, for practical purposes the 50 μg dose orally will not distinguish between megaloblastic anemias due to folic acid deficiency and those resulting from a deficiency of vitamin B₁₂. In order to encompass all patients, daily doses in a range between 100 μg (12) and 400 μg (21) appear to be necessary.

SUMMARY

A case of megaloblastic anemia due to pure folic acid deficiency is reported. Small oral doses of synthetic folic acid, 50 μg given daily, were sufficient to alleviate the symptoms and to cause a rise of the platelets and white blood cells, but did not initiate improvement of the anemia. This may be indicative of the different metabolic activities manifested by the specific marrow cells.

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Problems in Diagnosis of Intracranial Disease Among the Aged

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As the population ages, with more and more people living beyond the sixth decade, the incidence of neurological disease in this group proportionately mounts. Too often, the diagnosis of "stroke" or "hardening of the arteries" is made without definite evidence. Due to the obvious factor of age, clinicians are very prone to combine localization of pathology and etiology by these terms. The purpose of this paper is to underscore the pitfalls which one may encounter in evaluating cerebral manifestations among the aged.

A major problem is an evaluation of the possibility of intrinsic vascular disease versus a space-occupying lesion. Many use the clinical rule that vascular pathology usually starts suddenly and mass lesions are gradual in onset. The clinical course of the former consists of maximal symptomatology immediately, with gradual remission (if there is no fatal outcome). Space-occupying lesions, on the contrary, begin gradually and progress inexorably until diagnosed.

In terms of the clinical neurological manifestations, there does not appear to be any finding in either the mental status, the cranial nerves, the motor defects, reflex changes or sensory abnormalities which can help delineate an etiological process. However, it has been stated that a fluctuating level of consciousness is usually seen in patients suffering from subdural hematoma.

With respect to laboratory data, other than blood and urinalysis, some specific laboratory aids are considered helpful. Plain skull x-rays may reveal abnormal calcification, lytic lesions, shift of a calcified pineal gland, and enlargement of the sella turcica. An electroencephalogram may show a focus of abnormally slow activity and, in "diffuse vascular" disease (the type which is associated with progressive mental deterioration in the senium), the electroencephalogram may be normal. A lumbar puncture can give information such as the presence of bleeding or xanthochromia. The latter is well known to occur in subdural hematoma. Pleocytosis occurs in infections, neoplasms adjacent to the ventricular system, carcinomatosis, leukemia and, frequently, after a pneumoencephalogram. Increased spinal fluid protein is highly suggestive of neoplasm.

Special neurological procedures, such as pneumoencephalography and angiography, can be of definitive value in clarifying etiologic processes. However, many physicians fear the morbidity of these procedures, especially in an older age group.

This is a study of 169 patients 70 years of age or over who were admitted to the neurological service and seen in consultation by an attending neurologist during a twelve-month period, 1961-1962. 112 patients were diagnosed as having encephalopathy due to vascular disease, or presumed to have vascular disease

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inasmuch as no other etiology was discovered. 24 of these patients had no focal manifestations. There were 35 patients who suffered from space-occupying lesions (27 had neoplasms and 8 had subdural hematomas). Five patients had drug intoxication, 2 suffered head injuries, and 1 patient had an acute infection of the central nervous system.

The following case reports are indicative of the clinical problems which have been encountered in the experience of this neurological service.

Case 1. A 75 year old right-handed woman was well until she fell, for unknown reasons, down a flight of stairs, striking her forehead. There was no definite history of loss of consciousness. She was well until five weeks after the accident, when she began to have unsteadiness of gait and weakness of the right leg. She developed insomnia, depression and forgetfulness, especially for recent events. Her mental deterioration rapidly increased to the point where she was incontinent of urine. Eight weeks after the injury, she was hospitalized.

The general medical examination was normal.

Neurological Examination: Mental status—there was an organic mental syndrome and her spontaneous speech was at times incomprehensible. Cranial nerves—there was a horizontal nystagmus on right and left lateral gaze and a right central facial weakness. Motor status—no significant abnormalities. Reflexes—the deep tendon reflexes were equal and active. No Babinski sign was noted. Sensory examination—this could not be evaluated because of her mental status.

Laboratory Data: The blood count and urinalysis were normal. Blood glucose was 136 mg%. Blood urea-nitrogen, proteins, calcium, phosphorus, cholesterol, uric acid were normal. Blood serology was negative. A lumbar puncture revealed xanthochromic fluid, initial pressure 130 mm. There were 100 polymorphonuclear cells and 800 red blood cells per cm. Spinal fluid sugar was 119 mg%; chloride 92 meg/l; protein 101 mg%. Chest and plain skull x-rays were normal. An electroencephalogram revealed 3-5 per second activity throughout the entire left cerebral hemisphere, accentuated in the left temporal area. A left carotid angiogram revealed a vascular tumor in the posterior parietal region, extending into the region of the corpus callosum. A pneumoencephalogram revealed the same mass extending across the corpus callosum, involving the right parietal area.

Course: The patient progressively deteriorated and died twenty-six days after admission. Post mortem examination revealed a glioblastoma multiforme involving both cerebral hemispheres in the parietal areas.

Comment: The history of the fall two months prior to hospitalization suggested the possibility of a subdural hematoma. The 100 polymorphonuclear cells in the spinal fluid widened the diagnostic probabilities to include a brain abscess, although this was thought less likely because of the high spinal fluid sugar. The correct diagnosis was established by angiography and pneumoencephalography. It is noteworthy that in spite of her age and the massive cerebral pathology, she had no complications from the procedures. Since there was bilateral cerebral involvement and the short history, as well as the vascular stain, indicating a malignancy, surgery was not considered efficacious.

Case 2. A 70 year old man was well until fourteen months prior to admission, when he began to have episodic jerking of the left hand lasting "a minute or so." Shortly thereafter, generalized convulsions ensued and he was placed on Dilantin. In the following months, his memory became progressively worse and there were marked personality changes. It was noted that he began to sleep excessively. Two weeks prior to admission, he developed numbness of the left hand and then became unconscious. He was incontinent of urine at this time and claimed that for a few days thereafter he had numbness of the left hand and left face. The past medical history was significant in that he had been suffering from diabetes mellitus for eight years and was being treated with Orinase.

The general medical examination was normal; his blood pressure was 170/95.

Neurological Examination: Mental status—he had a severe organic mental syndrome; he had difficulty following simple commands and naming the days of the week. He could not spell “cat” backward. There was a right-left disorientation. Cranial nerves—there was a questionable left central facial weakness. Motor status—no significant abnormalities other than a broad-based gait. Reflexes—deep tendon reflexes were equal and active; the ankle reflexes were hypoactive. Sensory examination—this could not be evaluated because of the mental status.

Laboratory Data: The blood count was normal. A urinalysis revealed a ++ albuminuria. The sedimentation rate was 62. A fasting blood sugar was 238 mg%. Total cholesterol was 530 mg%. Blood urea-nitrogen, proteins, calcium, phosphorus, alkaline phosphatase and acid phosphatase, uric acid, cephalin flocculation test, prothrombin time were normal. The blood serology was negative. A lumbar puncture revealed clear, colorless fluid under normal pressure. Two hundred red blood cells were noted. Spinal fluid protein was 44 mg%. Chest and plain skull x-rays were normal. An electroencephalogram showed 2-6 per second slow activity in the left cerebral hemisphere, accentuated posteriorly. A left carotid arteriogram was normal. A pneumoencephalogram revealed moderate hydrocephalus, with generalized dilation of the ventricular system.

Course: The patient has done fairly well on anticonvulsant medication.

Comment: The history of the seizure disorder, with a focal onset and progressive mental deterioration, raised the question of a space-occupying mass. The very slow activity in the electroencephalogram is also more often seen in gross focal pathology. However, after fourteen months, there were no definite focal neurological findings and the cerebrospinal fluid was normal, indicating that perhaps a mass lesion may not be present. The final diagnosis could not be established until pneumoencephalography. In the experience of this neurological service, focal or generalized seizures beginning in the elderly age group are not an uncommon finding in patients who, upon investigation, do not have mass lesions.

Case 3. A 70 year old man was well until he suddenly developed a grand mal seizure, after which the left side of the body was noted to be paralyzed. He was hospitalized elsewhere and a lumbar puncture was reported as normal. An electroencephalogram revealed right-sided dysfunction. A pneumoencephalogram was also normal. His hemiparesis improved nine days after the onset of his illness and he was placed on anticoagulation therapy. Two days later, because his condition worsened, he was transferred to this hospital. At this time, he admitted to having headaches since the beginning of his illness. During the previous three months, he had a chronic cough, associated at times with hemoptysis.

The general medical examination was normal. Temperature was 101.6°F. on admission.

Neurological Examination: Mental status—there was an organic mental syndrome. Cranial nerves—he had a left homonymous field defect. There was horizontal nystagmus on right lateral gaze. The left corneal reflex was absent. There was a left central facial weakness. Motor status—there was a left hemiplegia and a questionable weakness of the right extremities. Reflexes—the deep tendon reflexes were increased in the left extremities. No Babinski sign was noted. Sensory examination—this was unreliable due to his mental status, but he did make errors in the left hand, which he did not make in the right hand, such as misidentifying objects placed in the left hand. There was extinction to pin stimulation on the entire left side of the body.

Laboratory Data: Blood count—the hemoglobin was normal; the white blood count was 11,200; 55% segmental cells; 2% band cells; 27% lymphocytes; 6% monocytes. The sedimentation rate was 44 mm. Urinalysis, fasting blood sugar, blood urea-nitrogen, proteins, uric acid, calciums, phosphorus, cholesterol, cephalin flocculation test, alkaline phosphatase were normal. The prothrombin time was 55.5 seconds, as compared to 13 seconds controlled. Chest and plain skull x-rays were normal. An electroencephalogram revealed severe slow activity in the right cerebrum, accentuated in the temporal area. A lumbar puncture revealed xanthochromic spinal fluid, with an initial pressure of 80 mm. There were 273 polymorphonuclearcytes and 190 lymphocytes. Spinal fluid protein was 290 mg%. A right carotid arteriogram revealed an avascular space-occupying mass in the temporoparietal region.

Course: This patient progressively deteriorated and died on the third hospital day. A post mortem revealed a brain abscess in the right occipital and parietal areas.

Comment: The sudden onset of a left hemimotor-sensory syndrome, normal lumbar puncture and pneumoencephalogram seemed to indicate vascular disease. He became worse two days after being placed on anticoagulation and the prothrombin time of 55 seconds raised the possibility of a complicating intracranial hemorrhage (1). Also, because of the history of cough and hemoptysis, and the elevated sedimentation rate, metastatic carcinoma to the brain was also seriously considered. The pleocytosis in the spinal fluid has been seen in malignancy, as well as infection, and the former was thought perhaps to be more likely, especially since brain abscess is relatively uncommon. Unfortunately, his condition was so poor upon admission and worsened so rapidly that he could not be treated in time.

Case 4. A 70 year old man was well until two and a half weeks prior to admission, when he suddenly felt a slight weakness in the right leg. There were no other neurological symptoms other than a tremor of the left hand, which had been present for approximately seven years.

A general medical examination was normal.

Neurological Examination (ten days after the onset of weakness): Mental status—normal for his age, except it was thought that he had an anomia. Cranial nerves—there was a slight right central facial weakness. Motor status—he dragged the right leg and the right arm had lost its associated movement on walking. Tapping with the right foot was slower than the left. There was a definite weakness of the right upper extremity. There was also noted slight “Parkinson” tremor bilaterally. Reflexes—the deep tendon reflexes were equal and active. No Babinski sign was noted. Sensory examination—all sensory modalities were normal, except that there was extinction on the right side on double simultaneous stimulation.

He was re-examined five days later; at this time, there was definite difficulty in understanding simple commands and in finding words. There was also a marked change in his personality. Because of this progression, he was hospitalized.

Upon hospitalization the general medical examination was normal.

Neurological Examination (at hospitalization): Mental status—there was an organic mental syndrome and evidence of a motor and sensory aphasia. Cranial nerves—he had a right homonymous field defect and a right central facial weakness. Motor status—the deep tendon reflexes were equal and hypo-active, except for the right knee and ankle reflexes, which were increased. The right plantar response was defective. Sensory examination—he had a right-sided hypesthesia and hypalgesia. On double simultaneous stimulation, there was extinction of the right side.

Laboratory Data: Blood count, urinalysis, sedimentation rate, two-hour postprandial blood sugar, urea-nitrogen, calcium, phosphorus, proteins, alkaline phosphatase, prothrombin time were normal. A lumbar puncture revealed clear, colorless fluid, under normal pressure. No cells were noted. Spinal fluid protein was 28 mg%. Spinal fluid serology was negative. Chest and plain skull x-rays were normal. An electroencephalogram indicated left cerebral dysfunction manifested by diffuse bursts of 1.5 to 4 per second activity. A left carotid arteriogram revealed a large subdural hematoma.

Course: The patient was not operated upon, but was observed carefully over the next twenty days. He slowly but definitely improved. At this time, a repeat carotid arteriogram was performed, which revealed the same hematoma, which was slightly smaller than demonstrated on the previous angiography. Since he had improved, it was decided to discharge him and observe him carefully for any further developments.

He was re-admitted one month later, because, for three days, he had developed confusion and recurrent weakness of the right extremities. His neurological condition was about the same as when he was admitted the first time.

A right carotid arteriogram revealed the subdural hematoma to be the same as when discharged.

A neurosurgical opinion concurred as to the efficacy of surgery.

A craniotomy, with evacuation of the clot, was performed. The patient did well for the first twenty-four hours. He was alert, responsive and only had a mild hemiparesis post-operatively. However, the second day postoperatively, he developed a temperature of 101°F. and became drowsy. He did not do well and developed a severe right hemiparesis. Two days later, his mental picture improved and he became relatively alert. Over the next two weeks, he did fairly well and it was noted there was slight improvement in his aphasia, as well as some spontaneous movement of the lower right extremity, which had become plegic following surgery. However, he began to run a temperature and, on the twenty-first postoperative day, this spiked to 104°F. It was thought that the focus of the infection was in the urinary tract. In spite of antibiotics, his condition deteriorated; he had difficulty maintaining blood pressure and he died one month following surgery. Post mortem was not obtained.

Comment: Although the onset of his condition was sudden, as in intrinsic vascular disease, the rapid progression seemed to indicate a mass lesion. A carotid occlusion, with subsequent hemiedema, may present a similar picture (2). The normal cerebrospinal fluid findings are not rare in subdural hematoma. The absence of trauma in this condition is reported in almost 50 per cent of the cases and is similarly so in the experience of this hospital. Recently, the spontaneous remission of subdural hematoma has been reported and this patient was treated for a time conservatively (3). It is now thought that indications for surgery depend more on the patient's clinical state and course, rather than the presence of the hematoma per se. This may portend a critical change in management, especially in the aged, who do not do as well as younger patients following major surgery and general anesthesia. Although this patient was in good clinical condition prior to surgery and apparently had a successful operation, tragically, a complicating infection led to a fatal outcome.

Case 5. A 70 year old woman was in good health until she fell, for unknown cause, down a flight of stairs, suffering a severe head injury. Within an hour thereafter, she developed a paralysis of the left side of the body and was hospitalized elsewhere. A lumbar puncture at that time revealed bloody fluid. Her condition improved over a period of two weeks and then fluctuated downhill, until she became comatose. At this point, she was transferred to this institution.

A general medical examination was normal.

Neurological Examination: Mental status—the patient was in deep stupor but did respond to painful stimuli. Cranial nerves—the eyes were deviated conjugately to the right. The oculocephalic reflexes were normal. There was a left facial weakness. Motor status—there was a flaccid left hemiplegia. Reflexes—the deep tendon reflexes were absent throughout; there were bilateral Babinski signs. Sensory examination—the patient responded minimally to painful stimuli.

Laboratory Data: A right carotid arteriogram was performed immediately and revealed a large subdural hematoma.

Course: A craniotomy was performed and the clot was evacuated. The patient gradually improved and was finally discharged with a residual severe organic mental syndrome and a left hemiparesis.

Comment: There was no question of an acute intracranial hemorrhage at the onset of her illness. It was not known whether this was due to the head injury or whether the accident was due to the development of a sudden hemorrhage. The rapid deterioration in her neurological state following the acute illness indicated that something new had occurred. There was the possibility, of course, of recurrent bleeding, as well as the possibility of a subdural hematoma. Subdural hematomas following intracranial bleeding are quite unusual, but have been reported (4). A lumbar puncture was not performed. This reflects the difference of opinion between neurologists and neurosurgeons. The patient was admitted directly to the neurosurgical service and it is felt by the latter that a spinal tap might be dangerous. Recent papers by neurologists, however, indicate that complications following lumbar puncture are relatively insignificant and the information obtained may be critically helpful in managing the patient (5, 6).

Case 6. A 73 year old man was well until he had a sudden episode in which his speech became incoherent and he developed confusion as to time and place. He became nauseated and vomited on several occasions. An examination by his physician revealed an "aphasia" and weakness of the right side of his body. He was hospitalized one week after the onset of the neurological symptomatology.

The general medical examination was normal.

Neurological Examination: Mental status—the patient was very apathetic and confused, and it was very difficult to communicate with him. It was not clear whether he had an aphasia or not. Cranial nerves—there was a left homonymous field defect. Motor status—there was a questionable slight motor deficit of the left extremities. Reflexes—the deep tendon reflexes were absent throughout. There was a left Babinski sign. Sensory examination—there was a distinct sensory defect in the left extremities, with astereognosis in the left hand. His neurological status rapidly deteriorated and, upon admission two days after the above examination, he was quite stuporous. In addition to the findings noted in the neurologist's office, there was a weakness of conjugate gaze; the eyes drifted to the right. Because of the progressive intracranial disease, although vascular pathology was considered most likely, a subdural hematoma was also suspected.

Laboratory Data: Urinalysis, blood count, sedimentation rate, blood sugar, urea-nitrogen, calcium, phosphorus, sodium, potassium, carbon dioxide, chlorides, proteins, alkaline phosphatase were normal. Chest and plain skull x-rays were normal. A lumbar puncture revealed xanthochromic fluid under an initial pressure of 310 mm of fluid. There were 2,820 red blood cells. Spinal fluid protein was 280 mg%. An electroencephalogram revealed diffuse slow activity, as slow as a half a cycle per second. The left side was more involved than the right.

Course: The patient's condition rapidly deteriorated during the first twenty-four hours after admission. A right carotid arteriogram was normal. The following morning, a left carotid arteriogram was performed, which was also normal. The patient continued to go downhill and died the following morning. Post mortem examination (unfortunately limited to the head) revealed metastatic melanoma involving both cerebral hemispheres, the brain stem, and the cerebellum.

Comment: The sudden onset seemed to indicate intrinsic vascular pathology. However, because of the history of bilateral cerebral disease, a subdural hematoma was also considered. The cerebrospinal fluid findings made this latter possibility more likely, to a degree that an emergency carotid arteriogram was performed in the middle of the evening. Metastatic carcinoma is usually seen on angiography and as many as six lesions have been demonstrated by a single carotid arteriogram. This case was only diagnosed by autopsy. Not infrequently, angiography has to be repeated before a tumor stain is visualized. Patients can be erroneously diagnosed as suffering from vascular disease until subsequent re-evaluation demonstrates a malignancy. Therefore, when the latter etiology is suspected, it is wiser to observe the patient as "a brain tumor suspect" in spite of a normal angiogram and/or pneumoencephalogram.

Case 7. A 78 year old man was well until the day prior to admission. He awoke that morning with a headache and took two Doriden pills. He had an afternoon nap and awoke "groggy." However, he stayed up until eleven o'clock in the evening watching television. In the evening, he took "two Bufferin tablets" for a headache. The following day, about twelve o'clock, it was noted that the patient could not be aroused.

The general medical examination was normal.

Neurological Examination: Mental status—he was in deep coma. His respirations were rapid and deep. There were no unusual odors noted on his breath. Cranial nerves—pupils were round, regular, somewhat miotic. Motor status—there was a flaccid quadriplegia. No abnormal movements were noted. Reflexes—deep tendon reflexes were absent. No Babinski sign was noted. Sensory examination—he did not respond to painful stimuli.

Laboratory Data: Blood count, urinalysis, clotting time, prothrombin time, urea-nitrogen, blood sugar, calcium, phosphorus, cholesterol, sodium, potassium, carbon dioxide, chlorides

were all normal. A lumbar puncture revealed clear, colorless fluid under normal pressure. No cells were noted. Cerebrospinal fluid protein was 140 mg%. Chest and skull x-rays were normal. An electroencephalogram was normal. He was maintained on intravenous fluids, with the addition of Levo-phed, because of difficulty in maintaining normal blood pressure.

Course: The diagnosis of drug intoxication, either aspirin or even barbituates, was considered most likely. The patient remained in deep coma for over forty-eight hours and the abnormal cerebrospinal fluid protein raised the possibility of a mass lesion, specifically a subdural hematoma. A left carotid arteriogram was normal. Twenty-four hours later, the patient began to respond and gradually improved. When he was well, it was learned that he had been depressed. He began to hoard barbituate tablets and finally took an overdose of sleep medication.

Comment: Although, from the onset, drug intoxication was considered most likely, the absence of any history of an emotional disorder, the prolonged coma and the high spinal fluid protein raised the possibility of a subdural hematoma. A normal electroencephalogram, which can occur in drug intoxication, has also been obtained in patients with a subdural hematoma, and, therefore, was not too helpful. Angiography was essential in ruling out this latter condition and, again, it is noteworthy that this 78 year old patient had no ill effects from the procedure.

Case 8. A 73 year old man was known to have metastatic carcinoma to the lung. The primary lesion was unknown. He had been hospitalized previously because of dyspnea associated with a pleural effusion. On the day of admission, he lost his vision, asserting "everything went black for four to five hours." Vision gradually improved, but, because of persistent and progressive shortness of breath, he sought re-admission.

A general medical examination revealed a cachectic man, who was in severe respiratory stress with cyanotic nail beds. The examination of the chest revealed flatness to percussion over the entire left chest wall. The right lung field was clear. There was pain on palpation over the right posterior rib cage. He had a tachycardia of 120 per minute. There was an enlarged liver four fingerbreadths below the costal margin.

Laboratory Data: Hemoglobin 10.1 mg%; white blood count 9,800, with slight shift to the left. Urinalysis was normal, except for a trace of albumin. Sedimentation rate was 50. Serum proteins were 5.8; albumin 3.2; globulin 3.6. Alkaline phosphatase was 19.7. SGOT 68.

Course: Patient developed an organic mental syndrome in the hospital. He was then examined by a consulting neurologist, who noted no focal findings except a left Babinski sign. The sensory examination could not be done because of the organic mental syndrome. A neurological investigation was recommended.

The possibility of metastatic carcinoma to the brain, as well as intrinsic vascular disease, was considered. The patient suddenly became progressively worse, lapsed into coma and died. A post mortem revealed an intracerebral hematoma of the right frontal-parietal region, approximately 6 cm in diameter.

Comment: This case was not transferred to the neurological service, because it was thought that he surely had metastatic carcinoma to the brain. The presence of an intracerebral hematoma, which is not unusual at this age, was a surprise only because he suffered from cancer. This demonstrates that, at all times, all etiologies should be given due consideration and a patient should be completely worked-up.

Case 9. A 78 year old man was admitted with a history of severe low back pain of three weeks' duration and, for the week prior to admission, progressive confusion, lethargy and incontinence of urine and feces. The past history was significant in that he had had intermittent pain in the back for at least twenty years. A prostatectomy was performed in 1960 and, for five years, because of angina and irregular cardiac rhythm, he had been treated with quinidine and Peritrate.

The general medical examination revealed an acutely ill man. No definite abnormal findings were noted, except bilateral pretibial edema.

Neurological Examination: Mental status—he was lethargic and had an organic mental syndrome. Cranial nerves—no abnormalities except a dysarthria. Motor status—there was no focal weakness, no dyskinesiae, and muscle tone was normal. Reflexes—the deep tendon reflexes were equal and active, except the ankle reflexes were absent. There were bilateral Babinski signs. Sensory examination—could not be performed due to the mental syndrome.

Laboratory Data: A white blood count revealed a leukocytosis of 19,000, with a shift to the left. A urinalysis revealed a trace of albumin. Sedimentation rate was 59. Blood urea-nitrogen 114 mg%; creatinine 3.7 mg%; calcium 16.1 mg%. Blood sugar, phosphorus, proteins, alkaline phosphatase, sodium, potassium chloride were normal. A lumbar puncture revealed xanthochromic fluid; the protein was 74 mg%. The heart was enlarged on x-ray examination. Vertebral x-rays showed severe osteoporosis. An electroencephalogram revealed diffuse slow activity.

Course: In spite of intensive medical care, he steadily worsened and died on the seventh hospital day. An autopsy was performed, which revealed no definitive pathology in the brain.

Comment: The rapid history of alteration of cerebral functioning, as well as the abnormal cerebrospinal fluid protein, suggested a mass lesion. However, the blood chemistries indicated renal failure and possible hyperparathyroidism. In view of the major systemic dysfunctions, neurological procedures were not considered indicated. It is important to note that renal failure can produce a relatively rapid deterioration in an elderly person's mental state. The normal cerebral findings at post mortem are not uncommonly seen in patients that die of uremia (7).

Case 10. A 71 year old man slipped on a painter's scaffold ladder and struck his head against a wall, suffering severe head pain. His family relates that when he returned home from work, he was quite confused and had difficulty in talking. This mental state worsened over the next three weeks. An electroencephalogram performed on an out-patient basis revealed a severe slow wave focus in the left temporal region, and he was hospitalized.

The general medical examination was normal.

Neurological Examination: Mental status—he had a severe organic mental syndrome and definite aphasia. Cranial nerves—there was a right homonymous hemianopia and a right facial weakness. Motor status—there was clumsiness and weakness of the right arm and leg. Reflexes—deep tendon reflexes were equal and active. No Babinski sign was noted. Sensory examination—could not be done.

Laboratory Data: A blood count, urinalysis, bleeding and clotting time, serology, sedimentation rate, blood sugar, urea-nitrogen, proteins, alkaline and acid phosphatase were normal. A spinal tap revealed clear, colorless fluid under an initial pressure of 230 mm of fluid. No cells were seen. Protein was 30 mg%. Chest x-ray revealed a thymoma. Skull x-rays were normal. A repeat electroencephalogram revealed a severe left slow wave focus. A left carotid angiogram was normal.

Course: The patient was discharged. During the following year and a half, he has slowly improved.

Comment: The history was suggestive of the development of a subdural hematoma. This was not corroborated. Whether he suffered a cerebral injury or had a coincidental vascular lesion, which then caused the head injury, could not be determined. Another possibility was that he may have had a hemorrhage into the temporal lobe, but this also could not be confirmed. The slow wave focus is reported most often in gross lesions, but at least, by angiography, this was not the case.

Case 11. A 75 year old woman, three weeks prior to admission, fell down a flight of stairs, striking the left side of her head and suffering a severe head injury. Following the accident, she complained of right-sided headaches, unsteady gait and nausea. Her relatives thought her memory concomitantly worsened. The past history was significant in that she had been hospitalized two years previously for the treatment of pernicious anemia and diabetes mellitus, which had neurological manifestations—a diffuse radiculoneuropathy, as well as an or-

ganic mental syndrome. During that hospitalization, she had two grand mal convulsions and an electroencephalogram revealed bursts of slow activity on the left side.

The general medical examination was normal, except for the presence of a small amount of dried blood in the right external ear canal. A cephalohematoma over the left parietal area was also noted.

Neurological Examination: Mental status—there was an organic mental syndrome. Cranial nerves—smell was defective in the right nostril. Optokinetic nystagmus was absent in testing from right to left and was also defective in testing from left to right. Motor status—the patient walked with a broad-based gait, with a tendency to fall to either side. The Romberg test was positive. There was no definite focal weakness. There was no dyskinesiae. Reflexes—the deep tendon reflexes were hypoactive throughout. No Babinski sign was noted. Sensory examination—it was difficult to evaluate her sensory status, but, on double simultaneous stimulation, she always extinguished the left extremities.

Laboratory Data: The blood count was normal. Urinalysis revealed a trace of albumin and 4 plus sugar. No acetone was present. Blood sugar, urea-nitrogen, serum proteins, calcium, phosphorus, alkaline phosphatase, creatinine were normal. A lumbar puncture revealed clear, colorless fluid under normal pressure; no cells were seen. The protein was 59 mg%. Chest x-ray demonstrated an enlarged heart. Skull x-rays were normal. An electroencephalogram revealed bilateral cerebral dysfunction, with numerous bursts of irregular 1.25-4 cps activity, most marked at the temporal area, and the left side more involved than the right, and this tracing was much more abnormal than the one taken two years previously.

Course: A neurological examination repeated a week after admission revealed similar findings, except the left hemisensory syndrome was more definite and position-sense abnormalities were noted in the left hand. A right carotid angiogram revealed the presence of a subdural hematoma in the parietal region. Two days later, there developed more pronounced weakness of the left extremities. A left carotid angiogram at that point revealed the same shift to the left of the cerebral vessels. A craniotomy was performed and a subdural hematoma was removed. She did relatively well postoperatively, except for the development of convulsions on the fourth postoperative day. She steadily improved and was eventually discharged.

Comment: The long-standing background of mental changes and a seizure disorder made it very difficult to evaluate the etiology of the post-traumatic neurological condition at the time of admission. An initial impression of diffuse vascular disease with superimposed cerebral concussion seemed to have been substantiated by the relatively normal laboratory work-up, including the cerebrospinal fluid findings. However, a subdural hematoma was considered and proven to be present.

Case 12. A 70 year old man was admitted with a history of weakness of the left lower extremity for approximately four months. This weakness had occurred gradually and had progressed to a degree where he had marked difficulty in walking. It was also noted that he had had transient episodes of feeling drowsy and, on several occasions, he apparently "stared momentarily" for unknown reasons. It was thought, on one occasion, that his speech had become "confused." There were no other neurological symptoms. The past history was significant in that he was a sufferer, for twenty-four years, from diabetes mellitus and was taking protamine zinc insulin, 20 units a day.

The general medical examination was normal.

Neurological Examination: Mental status—there were no significant abnormalities. Cranial nerves—there was a left central facial weakness. Motor status—he had a left hemiparesis, arm and leg equally involved and weak, but proximal function more impaired than distal function. There was no abnormal tone noted. There were no dyskinesiae. Reflexes—the deep tendon reflexes were equal and active. There was a left Babinski sign. Sensory examination—this was normal.

Laboratory Data: The blood count was normal. The urinalysis revealed a one plus albuminuria. A fasting blood sugar was 154 mg%. Blood urea-nitrogen, serum proteins, prothrom-

bin time were normal. A lumbar puncture revealed clear, colorless fluid under normal pressure. 290 red blood cells were noted. The cerebrospinal fluid protein was 26 mg%. Chest and skull x-rays were normal. An electroencephalogram revealed bursts of irregular 2-5 cps activity in the right temporal area. A right carotid angiogram was normal.

Course: The patient was discharged unchanged and has since been relatively stable.

Comment: This patient had a relatively rapid progressive hemimotor syndrome and was initially thought to have a mass lesion, either neoplasm or subdural hematoma. The neurological work-up was entirely normal other than the electroencephalogram. Presumably, this patient may have had intrinsic vascular disease, and thus demonstrates how such a possible etiology can simulate a space-occupying lesion.

Case 13. A 73 year old man developed progressive impairment of memory and behavioral changes, over a nine-month period. It was stated he had become somewhat childlike. In the month prior to neurological examination, he developed difficulty in walking and needed to hold onto objects for support. There was a tendency to veering and he fell to his knees on several occasions. His speech became slurred and he had difficulty in articulation. His hearing had been bad for "many years."

Neurological Examination: Mental status—the patient seemed oriented and clear. The immediate memory seemed intact. He was able to calculate rapidly. Cranial nerves—there was a left homonymous field defect. This was more pronounced in the right eye than the left, and more distinct in the inferior quadrant as compared to the superior quadrant. There was a slight left facial weakness. Motor status—there was a drift downward of the left upper extremity, with both arms outstretched. There was incompleteness of performance of finger to nose testing on the left. Rapid alternating movements were slow. There was no manifest gross weakness of the extremities. Reflexes—the deep tendon reflexes were equal and active. No Babinski sign was noted. Sensory examination—this was normal.

It was thought that the patient had a lesion in the right parietal-occipital region, and, although vascular disease was considered most likely, the possibility of a neoplasm was seriously considered because of the progressive nature of the disturbance in function.

One month later, he was hospitalized because of pulmonary edema. At that time, a lumbar puncture was performed, which was normal. Carotid angiography was recommended, but the internist thought the patient was too sick to undergo this procedure.

Five months later, he was rehospitalized because of urinary retention. There had been progressive weakness of the left side, with further deterioration of the mental status. A repeat lumbar puncture revealed clear, colorless fluid under normal pressure and a protein of 81 mg%. Chest x-ray was normal. Skull x-rays showed the pineal markedly shifted right to left. An electroencephalogram revealed 1-2 cps activity in the right temporal region, monophasic and polyphasic spikes in the right occipital area. A right carotid angiogram revealed a neoplasm in the parietal-occipital region.

Course: Because of his general poor medical condition, he was given radiotherapy rather than subjected to surgery.

Comment: Although the diagnosis of vascular disease was thought most likely, the relatively rapid progression over a nine-month period with involvement of the visual system indicated a possible focal lesion in the right parietal-occipital region. Following his second admission, when it was noted that his neurological clinical condition had worsened, the cerebrospinal fluid protein had become abnormal and a mass lesion was strongly suspected and confirmed.

Case 14. An 83 year old woman was well except for progressive loss of hearing over "many years." She accidentally bumped her left temple against a glass knob and, although there was no loss of consciousness, she developed persistent frontal head pain. Two weeks later, her visual acuity diminished in the left eye and she had a sensation of "seeing stars" in that eye. The stars seemed to move to the left. Three weeks later, she developed poor vision in the right eye and objects appeared blurred. By this time, the left eye was almost completely blind.

The general medical examination was normal for her age.

Neurological Examination: Mental status—this was normal for her age. Cranial nerves—smell was markedly decreased in the left nostril as compared with the right. In the left eye, there was no light perception. However, she saw images consisting of black and gray flowers which constantly moved. There was a dense cataract and the fundus could not be seen. In the right eye, there was a right nasal field cut, most marked in the upper quadrant. There was also some impairment of the temporal field in the right eye. The right disc was somewhat pale. The right pupil reacted to direct light, but did not react consensually. The left pupil did not react to light, but did react consensually. There was bilateral diminished hearing. Motor status—normal. Reflexes—normal. No Babinski sign. Sensory examination—normal for her age. A bruit was heard over the left carotid artery.

Laboratory Data: A blood count revealed a leukocytosis, with 64% polys. A urinalysis was normal. Sedimentation rate was 69 mm per hour. Fasting blood sugar, urea-nitrogen, serum proteins, serum electrolytes and alkaline phosphatase were normal. Serology test was negative. A lumbar puncture revealed clear, colorless fluid under normal pressure. No cells were seen. The protein was 45 mg%. Chest and skull x-rays, including orbital view, were normal. An electroencephalogram revealed minimal abnormality of 4-7 cps activity diffusely present.

Course: The initial impression was that there was a possible lesion of the optic chiasm. However, one observer thought that there was a palpable, tender temporal artery. Because of the possibility of temporal arteritis, the patient was immediately started on intravenous adrenal corticotrophic hormone. After two to three days, she was continued on prednisone orally. A left carotid arteriogram was normal. A biopsy of the right temporal artery was performed, which revealed a granulomatous arteritis. The adrenal hormone was gradually reduced and she was discharged for further care at home.

Comment: This unusual case was considered to have a chiasma lesion most likely due to a tumor. The diagnosis of temporal arteritis is not often considered, especially in the absence of temporal pain. Progressive blindness without pain due to this condition has been reported (8). When vision is acutely impaired, close inspection and palpation of the external temporal arteries should always be made.

The cases described above demonstrate how difficult it is to make a proper diagnosis.

The mode of onset can be sudden in space-occupying lesions, as well as vascular disease. Moreover, the former can remiss temporarily, simulating a "stroke." Conversely, vascular disease of the aged may begin gradually and then progress, leading to the suspicion of the presence of a mass lesion. Of 27 patients who had neoplasms, 9 presented as "strokes." Five of the 8 patients who had subdural hematomas were not suspected of having such lesions. 28 of 112 patients who were discharged as having vascular disease were initially thought to most likely have space-occupying lesions.

The laboratory examinations have likewise been inconsistent.

Although lytic lesions, abnormal calcifications and a shifted pineal gland do occur, in most cases of space-occupying lesions the plain x-rays were normal. Chest x-rays have been of more value, since carcinoma of the lung (or elsewhere metastasizing to the lung) has been relatively common, especially when the cerebral manifestation is the first indication of a gross illness.

The electroencephalogram frequently shows slow activity in the region of the pathology, but, at no time can the abnormal electrical activity reflect an etiology. However, the electroencephalogram has been abnormal (including slow wave foci), but no demonstrable lesions have been found. Contrariwise, a normal rec-

ord has been obtained from patients with definite evidence of focal neurological pathology. In so-called "diffuse vascular disease," actually a wastepaper basket diagnosis (a preferable term is encephalopathy, cause undetermined), the electroencephalogram may be normal or may show mild to moderate diffuse slow activity. A conservative opinion is that the electroencephalogram can confirm the presence of cerebral pathology and may localize it. However, the record may be normal in spite of the presence of cerebral disease. Also, patients have been reported with false localization (the electrical focus and actual pathology residing in different hemispheres or far apart in one hemisphere) (9).

The lumbar puncture can give positive information, such as hemorrhage and xanthochromia. However, the fluid has been clear and colorless in patients who have bled, but whose lesions have not had time to extend into the subarachnoid space or ventricular system. Manometric determinations are not reliable—many patients with space-occupying lesions have normal pressure. Of course, this may reflect early investigations for such lesions before they begin to raise the intracranial pressure. In this group of patients, almost all had no increase in white blood cells. Red blood cells, crenated versus fresh, were usually consistent with the presumed time of onset of hemorrhage. The cerebrospinal fluid protein was of help in space-occupying lesions, in that it was frequently elevated. But there were false positive findings. Theoretic explanations have been offered, such as the possibility of increased protein due to a concomitant illness such as diabetes mellitus or due to a possible chronic (and incidental) compression of the spinal cord by herniated discs or cervical spondylosis. Also, there were patients with mass lesions whose cerebrospinal fluid protein determinations were normal.

The pneumoencephalogram and carotid angiogram were of major importance in elucidating the diagnoses. However, at times, these procedures can be normal and then, when repeated as a patient's condition progresses, may reveal a mass lesion. Infiltrative gliomas especially may be missed on an initial work-up. Not infrequently, patients present with focal findings, especially focal seizures, and only diffuse atrophy and dilatation of the ventricular system is seen. The important question of the risk of doing these procedures can only be answered by noting firstly that elderly patients can undergo these tests without untoward effect. Secondly, although morbidity exists and is higher in the older population, the indications of a pneumoencephalogram or carotid angiogram should be the total clinical problem. Each case must be evaluated individually. Management, including possible surgery, and intelligent prognosis can best be accomplished with as much information as possible. Carotid arteriography has recently been of inestimable value in the diagnosis and management of subdural hematoma. It is now feasible to observe such patients, many of whom have blood clots which spontaneously remiss. This is a distinct advantage in an age group which does not do as well as younger patients following intracranial surgery.

The impression of the above-mentioned inconsistencies must raise doubt as to the ease of making a proper diagnosis. The illustrative cases emphasize the problem. The aged do present major difficulties in diagnosis and the fact of the high incidence of vascular disease does not necessarily aid the clinician. One may readily ask the questions: Does one investigate every aged patient who has evi-

dence of cerebral disease? Is there any indication as to when neurological work-up should be recommended?

It is important to note one element, which is consistent throughout most of these 169 cases. Most of them gave a history of recent—weeks to a few months (and frequently sudden)—alteration of cerebral function. In slow, progressive mental deterioration, associated with aging, the history usually goes back “years.” *Whenever the alteration in mental function is relatively recent*, the clinician should be alerted to the possibility of gross structural changes. The etiology of such dysfunction can only be determined by a complete neurological diagnostic work-up. When such a study should be performed is a matter to be decided by the neurologist in each case. There are many factors, such as the general medical condition, the severity (and potential morbidity) of a neurological deficit (especially if the dominant hemisphere is involved), and, though not often stressed, the feelings and thoughts of relatives.

As time increases the neurologist's experience, many note that relatives are less and less willing to be satisfied with opinions based on statistical probabilities.

CONCLUSION

It is difficult to determine the etiology of cerebral disease of the aged on the basis of mode of onset, clinical course, and basic laboratory procedures, including plain x-rays, electroencephalography and lumbar puncture.

Complete neurological investigation, including pneumoencephalography and/or angiography, is feasible in the aged. Potential morbidity must be weighed against the value of information to be obtained. Each case should be decided individually.

Elderly patients who develop relatively rapid alterations in mental functioning are highly suspect of having gross structural changes due to neoplasm—either primary or secondary, subdural hematoma, infection, toxic-metabolic disturbances, as well as intrinsic vascular disease.

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Adenocarcinoma of the Small Intestine Occurring in a Case of Regional Enteritis

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Since the first classical description of regional enteritis in 1932 by Crohn, Ginzburg and Oppenheimer (1), the disease has been recognized with increasing frequency. Its clinical and pathological manifestations have been well documented with extensive follow-ups in a large number of cases. In recent years there have been six isolated case reports of carcinoma of the small bowel associated with regional enteritis (2 through 7) and, in view of the extremely low incidence of primary carcinoma of the small intestine, the association may be significant. The occurrence of adenocarcinoma of the colon in chronic ulcerative colitis seems to be a function of time, with frequency established in various series from 5 to 7 per cent in cases followed more than ten years (8). The following case report again associates chronicity of enteric disease with the development of adenocarcinoma.

CASE REPORT

T. R., a 51 year old Italian shoemaker, was admitted to the University Hospital on December 26, 1962, with a two week history of progressive abdominal cramps, distention, nausea and constipation. During the past several months he had been eating poorly and had reduced in weight from 145 to 126 pounds.

He had seen a doctor only occasionally for many years, but on close questioning he admitted having repeated episodes of intermittent midabdominal cramping pains for at least twenty-five years. In this interval, three gastrointestinal roentgenologic examinations were made with reportedly negative findings. He has had mild diarrhea and constipation off and on, and described some increased mucus in the stool but never passage of blood. In past years he had been treated for "spastic colitis" and was generally considered a neurotic person. However, throughout this time he never lost a day's work from his shoemaker shop.

Just prior to this hospital admission, a barium enema examination revealed some narrowing of the distal ileum and a peculiar, pouch-like dilatation of the ileum proximal to this which was interpreted as being a Meckel's diverticulum. Because of x-ray evidence that there was small bowel obstruction at this time, a small bowel series was not performed. Other than the patients' abdominal

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Editor's Note: With this paper the Journal of The Mount Sinai Hospital broadens its policy of publishing only papers based on Mount Sinai Hospital material or lectures delivered at the Hospital. Dr. Berman is a former member of our staff and in the future we will consider papers for publication from other alumni of the institution.

complaints, his past history had been entirely uneventful and he had never been hospitalized before.

Physical examination revealed a small, wiry, muscular man who evidently underwent recent weight loss. Vital signs were within normal limits. Despite his abdominal distress and cramps, he was spry, noncomplaining and cooperative. The abdomen showed potty distention in its lower half and high-pitched hyperactive bowel sounds were audible. There were no palpable masses. Rectal and proctoscopic examinations were negative.

Laboratory Data: Blood count, urinalysis and electrolyte determination were within normal range. A plain film of the abdomen confirmed the impression of mechanical distal small bowel obstruction.

Operative Findings: Because of the long history and the x-ray evidence of a narrowing of the terminal ileum, a preoperative diagnosis of regional enteritis with cicatricial obstruction was made. He was explored through a long right rectus muscle-splitting incision. The findings were those of classical regional enteritis involving the terminal four feet of the ileum. At a point 8 cm proximal to the cecum there was a dense cicatrix with complete stenosis of the lumen which admitted only the tip of a hemostat. There was eccentric dilatation of the small bowel proximal to this which accounted for the pouch-like structure seen on x-ray. There were areas of alternate dilatation and thickening of the bowel wall in the involved area with overgrowth of the mesentery and many large succulent mesenteric lymph nodes. There was no evidence suggestive of carcinoma on gross examination. The small bowel up to the ligament of Treitz disclosed no lesions. The remainder of the abdominal exploration was negative.

An ileocolic resection was performed including 5 feet of terminal ileum and the ascending colon, where an end-to-end ileo-ascending colostomy was performed.

The postoperative course was uneventful and the patient was discharged ten days after surgery. His only complaint after discharge has been the occurrence of mild diarrhea with 4 to 5 soft passages a day. He gained 20 pounds in weight in the month following discharge.

PATHOLOGY

The gross specimen consisted of a segment of ileum, cecum and ascending colon measuring 5½ feet in length. The only normal appearing bowel was located at either resection limit and measured 6 inches in length. The intervening bowel was characterized by alternating areas of constriction and dilatation (Fig. 1). The serosa throughout these zones showed fibrinous exudate and vascular congestion. The mesenteric lymph nodes were enlarged and boggy in consistency. In both dilated and constricted zones, the bowel mucosa showed a similar pattern, characterized by mucosal ulcerations which were irregular in size and shape and did not tend to conform to the long axis of the bowel or to have any predilection for the mesenteric attachment (Fig. 2). These ulcerations had an undermining effect on adjacent edematous preserved mucosa with the result that pseudopolypoid excrescences were present. The ulcerations were often deep, so

that even grossly the true muscle coat (*muscularis propria*) seemed exposed—an observation not substantiated on microscopic study.

Microscopic examination of the ulcerated areas in both small and large bowel showed denudation of the epithelium and replacement by a thin strand of fibrin. Beneath this, in the *lamina propria*, were dense collections of lymphocytes, plasma cells, and some eosinophiles. Just underneath this zone, there was

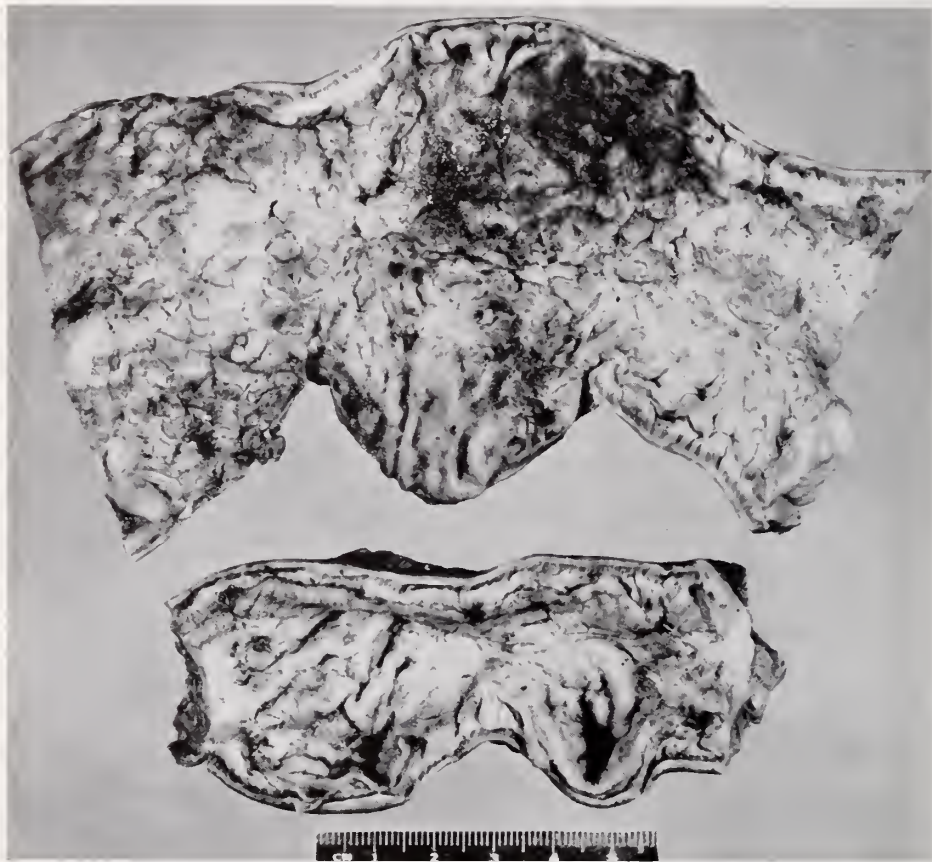


FIG. 1. Segment of small bowel. The upper specimen illustrates dilatation while the lower one is thickened and contracted.

abundant granulation tissue which extended as far as the *muscularis mucosa* (Fig. 3). This latter structure showed focal thickening of the muscular tissue. Small areas of cryptitis were occasionally noted and epithelial regeneration was seen on the margins of the ulcerations. The intact epithelium of the mucosa demonstrated a marked increase in the number of goblet cells. The submucosa was characterized by edema and nodules of mature lymphocytes and marked distention of the lymphatic vessels. Hypertrophy and nodules of lymphocytes were seen in the *muscularis propria*. The serosa showed evidence of edema,

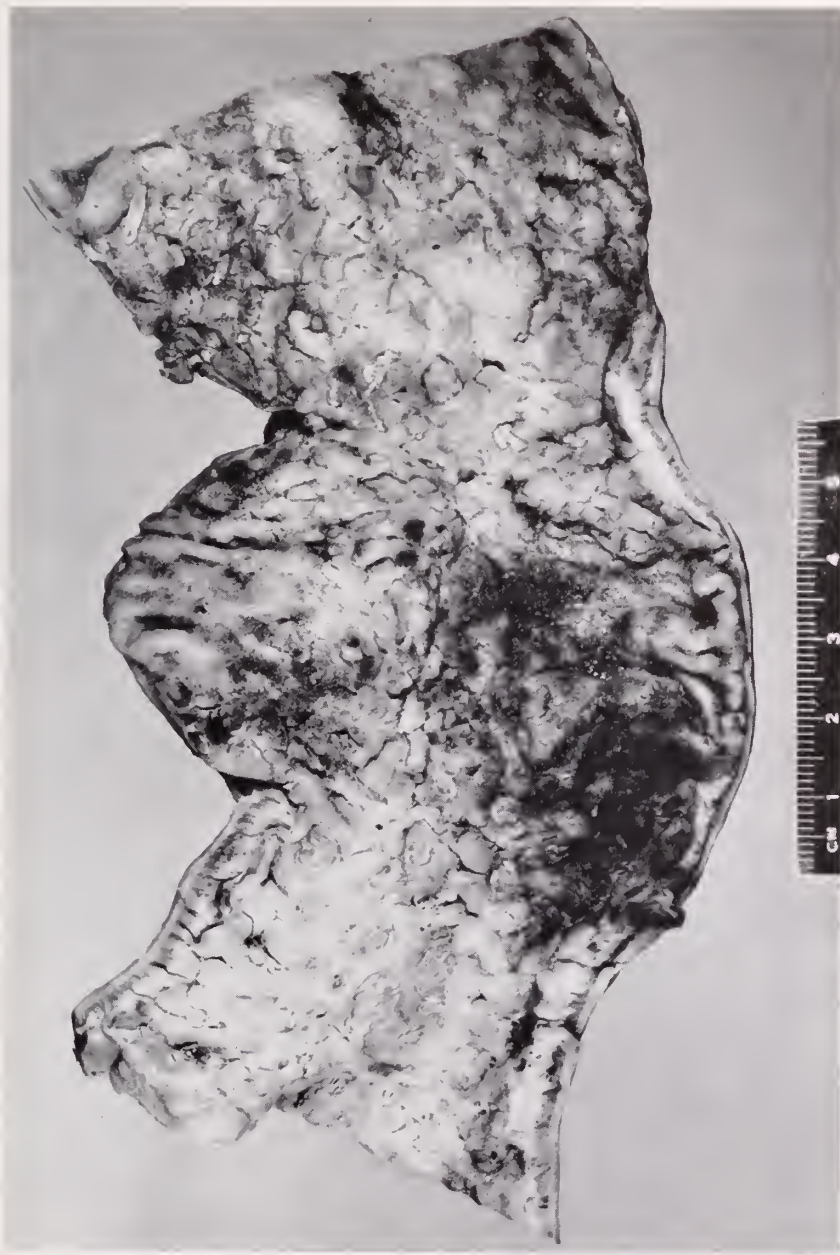


FIG. 2. Higher magnification of the dilated bowel segment shown in Fig. 1, showing numerous mucosal ulcerations and edema.

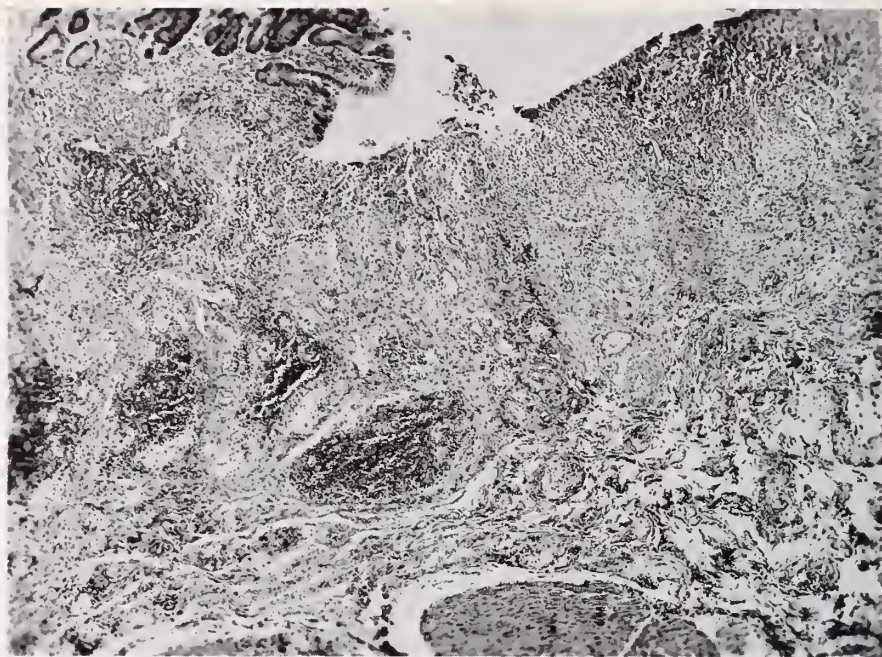


FIG. 3. Mucosal ulceration in small bowel penetrating muscularis mucosa. Lymphoid nodules are prominent in the muscular layer and in the serosa. ($\times 36$)

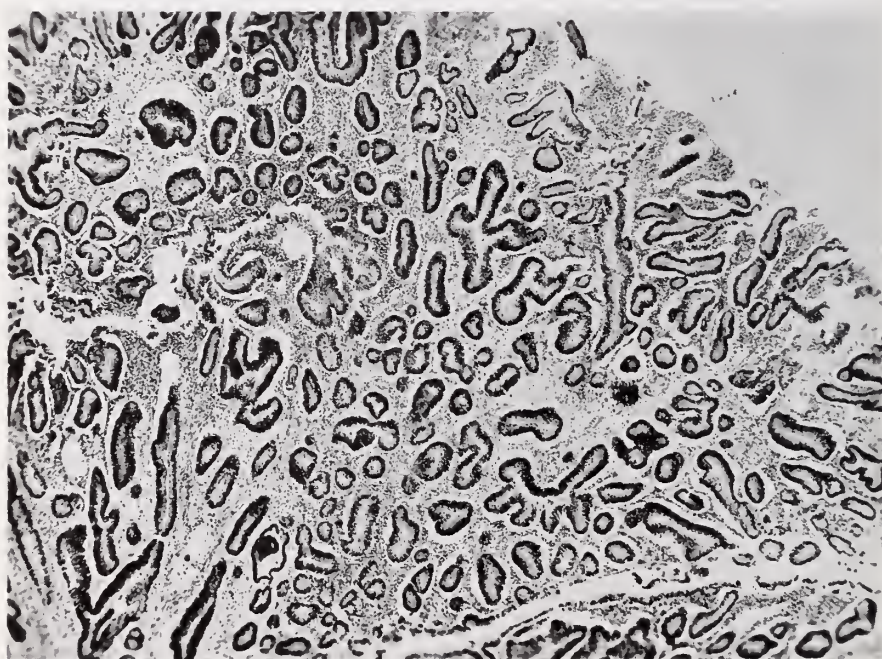


FIG. 4. Polypoid hyperplasia in the ileum with atypical histological characteristics. ($\times 39$)

lymphatic dilatation and nodules of lymphocytes. Granulomata or tubercles were not seen either in the bowel or in the mesenteric lymph nodes. The lymph nodes disclosed only sinusoidal lining cell hyperplasia and active germinal centers.

While these changes were representative of most of the bowel, one of the grossly thickened zones in the ileum had a most unusual appearance. A large zone of mucosal polypoid hyperplasia was present (Fig. 4). The pattern mimicked the gross configuration of the adenomatous polyp, but the epithelial cells were stratified, hyperchromatic and contained many mitotic figures. Broad zones

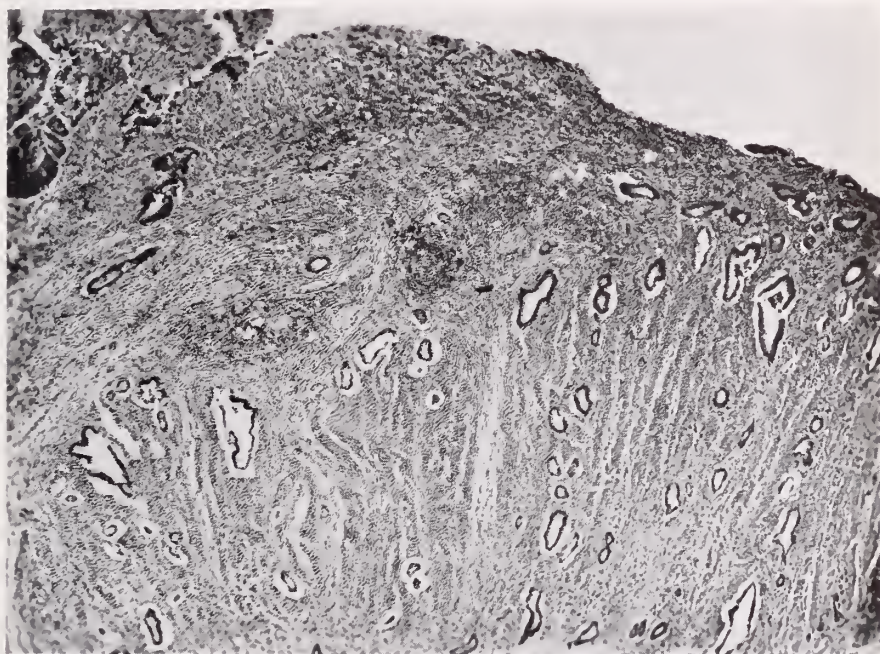


Fig. 5. Well-differentiated adenocarcinoma extending through entire thickness of small bowel. ($\times 44$)

of mucosal ulceration bordered on these areas and large numbers of well-differentiated glandular structures could be traced from one of these junctions through all coats of the bowel into the serosa (Fig. 5). Some of the glands appeared to lie within spaces suggesting lymphatic vessels, but close study disclosed these to be fixation shrinkage artefact. The diagnosis was a "well differentiated adenocarcinoma with serosal extension arising in small bowel showing typical changes of regional enteritis."

DISCUSSION

Ulcerative colitis does not evoke true polyp formation so that the incidence of carcinoma in this disease (5-7%) is presumed to be associated with the chronicity of the mucosal inflammation and its regenerative activity. The cases

in which malignancy develops usually have a history of ten to fifteen years of the disease. The case described here, of a carcinoma occurring in regional enteritis, shows changes suggesting that the neoplasm arose in association with polypoid hyperplasia. The tumor is extremely well differentiated, with the individual cells looking no more atypical than those cells in the polypoid hyperplasia zones. The pattern of growth, however, with serosal extension, makes a diagnosis of carcinoma in this case evident.

There are very rare instances of a carcinoma arising in association with regional enteritis. A report by Ginzburg *et al.* describes an anaplastic carcinoma of the jejunum which invaded the serosa and was not recognized at the time of surgical removal of the diseased jejunum (2). Seven months later, an exploratory laparotomy in this patient for epigastric pain disclosed metastatic carcinoma within the liver. The authors feel that this rare complication of regional enteritis, in contradistinction to the relative frequency of carcinoma in ulcerative colitis, may be due to the fact that carcinoma occurs frequently in the colon and only rarely in the small intestine.

A recent report by Hoffert *et al.* describes a well-differentiated adenocarcinoma arising in the terminal ileum of a forty year old man who had been subjected to an ileotransverse colostomy for ileitis two months previously (3). The tumor, like the one described in this report, infiltrated the entire thickness of the wall with extension into surrounding fat. Study of the photomicrographs of this case shows relatively little mucosal aberrations and nothing comparable to the polypoid changes seen in our case.

Kornfeld *et al.* describe an instance of adenocarcinoma occurring in regional jejunitis (4). The patient, a 36 year old woman with symptoms for eight years, had a carcinoma just distal to the ligament of Treitz with extension into the roots of the mesentery and upward over the pancreas in the vicinity of the superior mesenteric trunks. A retrocolic anastomosis between the transverse duodenum and the bowel immediately beyond the involved jejunum was performed and the patient survived for five months. At autopsy, an ulcerated polypoid carcinoma measuring 5 cm in length encircled the bowel just distal to the ligament of Treitz. The microscopic illustrations revealed a high grade adenocarcinoma which had spread to lymph nodes, lungs, liver and bones.

Bersack *et al.* describe a man who first came under observation at 26 years of age with abdominal pain, and loss of appetite and weight (5). The patient manifested intestinal symptoms over a nine year period during which he became progressively weaker and expired. At autopsy, there was a diffuse adenocarcinoma involving segments of the small intestine as well as cecum, ascending colon and distant metastases. No typical histologic evidence of regional enteritis could be identified, although nonspecific inflammation was present. The only suggestive histology was the presence of pyloric type glands in a section of ileum. The origin of the carcinoma was not established. It is our opinion that this case is not a convincing example of carcinoma arising in regional enteritis.

Weingarten and Weiss briefly describe a case of adenocarcinoma occurring in a 28 year old woman with a history of recurrent regional enteritis (6). This pa-

tient was operated upon three times because of persistent stricture formation in the space of five years. Twenty-six months after the second operation, the patient developed a series of spontaneous cutaneous fecal fistulas from a section of the involved enteritis. Thereafter, her condition deteriorated rapidly and, at the third operation, a section of extremely thickened small bowel with tumor nodules scattered through the abdomen was found. Pathological examination revealed chronic inflammatory disease with multiple strictures as well as adenocarcinoma involving all layers except the serosa.

Weingarten *et al.* report an adenocarcinoma occurring in the jejunum in non-specific granulomatous enteritis (7). The tumor occurred in a "by-passed" small bowel loop in a patient who had been under constant observation by one of the authors for twenty-one years. The tumor was a relatively high grade adenocarcinoma arising in the mucosa of the jejunum and extending into the muscularis. It had metastasized to regional lymph nodes, peritoneum, liver, lungs, uterus and ovaries.

The pattern of recurrent ulceration and regeneration over a long period of time common to chronic ulcerative colitis and regional enteritis may present an anlage for the development of carcinoma in these diseases. The increase in mitotic activity and the statistical chance for mutation associated with the reparative process may be significant factors in the development of carcinoma.

SUMMARY AND CONCLUSIONS

1. To date, there have been seven case reports of adenocarcinoma of the small intestine associated with regional enteritis.
2. It is suggested that chronic ulcerative disease of the intestine may set the stage for the development of carcinoma.
3. These clinical observations should be extended.

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Renal Glycosuria, Acidosis and Dehydration Following Administration of Outdated Tetracycline

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Recent reports by Gross (1) and Frimpter *et al.* (2) have described the onset of an acquired, adult-type Fanconi syndrome in patients being treated with tetracycline. The syndrome was characterized by diminished renal function, acidosis, proteinuria, glycosuria and amino-aciduria.

There is controversy at present as to whether the defect is caused by tetracycline per se, or by a toxic degradation product of tetracycline, anhydro-tetracycline.

The fifth such case to be described follows here. A review of the recent literature is also included.

CASE REPORT

A 31 year old single white female schoolteacher was admitted to The Mount Sinai Hospital on March 5, 1963, because of nausea, vomiting, weakness and dehydration of four to five days' duration.

She had been well all her life except for occasional exacerbations of asthmatic bronchitis. Several years previously, investigation of mild hirsutism revealed a normal menstrual history. The physical examination was negative except for slight clitoral enlargement. Laboratory values at that time revealed: hemoglobin 12.4 Gm%, fasting blood sugar 74 mg%, BUN 17 mg%, total protein, albumin, globulin and 17-ketosteroid levels normal. She was noted to be allergic to both penicillin and erythromycin.

Family history revealed that both grandmothers had diabetes mellitus and her only sibling, an older brother, had hyperglycemia on a glucose tolerance test.

On February 12, 1963, three weeks prior to admission, she developed an illness characterized by sore throat, generalized malaise, mild fever and productive cough. Without medical advice she began to take fresh tetracycline, borrowed from her roommate, one gram per day for four days, and noted improvement in her symptoms.

On February 20, 1963, her supply of fresh tetracycline ran out and she began to take one to two grams per day of tetracycline tablets that were at least 1½ years old and noted to be discolored.

She first sought the advice of a physician on February 25, and was noted to have a sinusitis and bronchitis with profuse nasal discharge, yellow sputum and audible and palpable rhonchi. A chest x-ray was normal. White blood cell count 11,000, BUN 13 mg%, 2 hour postprandial blood sugar 84 mg%. A urine analysis revealed specific gravity of 1.010, negative for sugar and protein, 3-5 white cells and 0-1 red cells per high power field. Serum total protein, albumin, globulin and

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alkaline phosphatase were normal. Her weight was 127 pounds. Novobiocin and tetracycline were prescribed. The patient did not take novobiocin until February 28, and stopped taking this drug after only two capsules because of nausea. However, she noted nausea even prior to taking novobiocin. She continued to take her discolored tetracycline tablets.

On March 1, she developed nausea, vomiting and weakness. There was no fever or abdominal pain. Nausea, vomiting and weakness continued to increase, and when she was next seen, slight abdominal discomfort was noted. The urine and stool were normal in appearance.

On March 5, the day of admission to hospital, the patient was found to have 4+ glycosuria (Testape) and 4+ albuminuria (sulfosalicylic acid).

On physical examination at the hospital she was a pale, and dehydrated white female who was markedly lethargic and weak. Blood pressure was 100/70 mm Hg, pulse 90 per minute, regular and weak. The temperature was 100.4°F. and respirations 22 per minute. The remainder of the physical examination was unrevealing, aside from the hirsutism.

Initial laboratory data revealed a hemoglobin of 16.2 Gm%, white blood count 18,800 per c mm with a left shift. On urine analysis the specific gravity was 1.028, acid reaction to litmus paper, 4+ albuminuria (sulfosalicylic acid) and 4+ glycosuria (Clinitest tablets) and 4+ acetoneuria (Acetest tablets). Microscopic examination revealed an occasional red blood cell, 10-12 white blood cells and an occasional granular cast per high power field. The BUN was 8 mg%, glucose 82 mg%, CO₂ 8.5 mEq/L, sodium 133 mEq/L, potassium 3.0 mEq/L, and chloride 111 mEq/L. The serum acetone was negative.

Hospital Course

Treatment of the acidosis and dehydration was begun with intravenous infusions of normal saline with the addition of potassium and 1/6 mol sodium lactate. Later potassium was given orally. Despite fluid and electrolyte replacement, her acidosis persisted until the ninth hospital day, and her serum potassium was low until the third hospital day. Proteinuria and glycosuria persisted until the nineteenth hospital day. Blood sugars were normal throughout the hospital stay. At the same time she produced an alkaline urine of low specific gravity.

An electrocardiogram on admission revealed depressed ST segments in leads II, III, and AVF, and a flat T wave in V₅ and V₆. Later in her course the ECG was normal.

On the fourth hospital day her BUN rose to 44 mg% and remained in this range until the ninth hospital day. At that time it was 20 mg% and has since remained normal.

During the first four hospital days, as a result of fluid replacement she regained nine of the twelve pounds she had lost.

An intravenous pyelogram and an upper gastrointestinal x-ray series were normal.

On the twenty-second hospital day her U_{max} (maximal urinary concentration)

TABLE I

Summary of Blood Counts and Chemistries Before, During and After Hospitalization

Hosp. Day	Date	Hgb. (in Gm %)	WBC (in 1000's)	BUN (in mg %)	Sugar (in mg %)	Sodium (in mEq/L)	Chlo- ride (in mEq/L)	Potas- sium (in mEq/L)	Carbon dioxide (in mEq/L)	Calcium (in mg %)	Phos- phorus (in mg %)
7 days prior to admis- sion	2-25	—	11.0	15	85*	—	—	—	—	—	—
1	3-5	16.2	18.8	8	82	133	111	3.0	8.5	—	—
2	3-6	14.6	26.4	16	42	145	125	2.4	8.5	—	—
3	3-7	—	—	19	85	148	123	4.0	13.5	10.0	0.9
4	3-8	10.3	18.0	44	95	152	125	4.5	15.0	—	—
5	3-9	9.3	14.1	47	112	133	118	3.8	15.0	9.7	—
7	3-11	9.7	15.6	46	100	146	121	3.5	17.0	—	—
9	3-13	—	—	20	78	145	116	3.8	21.0	10.2	2.0
12	3-16	12.1	16.5	—	115	—	—	—	—	—	—
14	3-18	—	—	19	79	150	112	4.2	18.0	—	—
16	3-20	—	—	—	92	141	97	4.2	16.0	9.9	2.8
18	3-22	—	—	—	85*	—	—	—	—	—	—
21	3-25	—	—	17	—	—	106	—	20.0	—	—
22	3-26	10.8	9.7	—	—	—	—	—	—	—	—
23	3-27	—	8.5	18	—	142	113	3.6	24.5	—	—
—	4-3	12.0	11.8	18	82*	140	105	—	23.0	10.0	—
—	7-27	—	—	15	98*	138	102	4.0	23.0	11.3	4.3

* 2 hour postprandial blood sugar in mg%. All other determinations are on fasting specimens.

TABLE II

Summary of Urine Analyses and Weights During Hospitalization

Hosp. Day	Date	Spec. Gravity	Reaction	Albumin	Sugar/ Acetone	RBC	WBC	Casts	Weight
1	3-5	1.028	Acid	4+	4+/4+	occ	10	6 gran	115
4	3-8	1.014	Alk.	3+	4+/0	occ	occ	0	124
5	3-9	1.010	Alk.	1+	2+/0	4-8	occ	occ	129
6	3-10	1.010	Acid	2+	0/0	2-3	4-5	0	127
7	3-11	1.010	Alk.	2+	Tr/0	occ	1-2	0	—
10	3-14	1.010	Alk.	2+	Tr/0	2-4	3-5	occ	118
12	3-16	1.012	Alk.	2+	Tr/0	0	3-4	occ	117
14	3-18	1.008	Acid	Tr	Tr/0	0	5-6	0	118
16	3-20	1.016	Alk.	1+	Tr/0	0	3-4	0	—
20	3-24	1.010	Alk.	0	0/0	2-3	10-12	0	—
24	3-28	1.028	Alk.	0	0/0	0	occ	0	122

was 492 mOsm/L, and 24-hour sodium and potassium excretions 60 and 40 mEq/L, respectively, indicating subnormal concentrating ability, presumably of tubular origin. By this time the patient was asymptomatic. On this day, at which time the urinalysis and chemistries were normal, a urine colony count grew out more than 200,000 colonies per ml, the organism later identified as E.

coli. Two other colony counts prior to this had been normal. Treatment was begun with chloramphenicol, 1 gram daily orally.

She was discharged after twenty-five days in hospital. When seen on two further occasions since discharge, she was found to be asymptomatic. Laboratory data are included in the tables.

DISCUSSION

In this case a 31 year old white female, with no previous history of renal disease developed marked nausea, vomiting, dehydration, acidosis, glycosuria and proteinuria while ingesting tetracycline. The tetracycline had been in the patient's home for about 1½ years and was discolored. Aside from amino-aciduria, which we were unable to document, the case resembles that of Gross (1).

The varied effects of tetracyclines on metabolic functions have been known for some time. Gabuzda (3) and Falloon (4) performed metabolic studies and found an increased nitrogen excretion even in the absence of significant pre-existent renal disease. Shils (5) noted a rise in BUN in patients treated with tetracycline. The higher the initial BUN, the higher was the rise. All patients developed a negative nitrogen balance, and this could be accounted for by the increase in nitrogen excretion. Along with the increased nitrogen excretion there was an increased excretion of both sodium and potassium in the urine. In some instances, the negative nitrogen balance induced by tetracycline could be counteracted by anabolic steroids. Gabuzda, Goeke *et al.* (3) administered chlor-tetracycline to a group of undernourished adults and in all cases found a loss in body weight, increased excretion of nitrogen in the urine, normal to increased fecal nitrogen, negative nitrogen balance and an increased serum NPN.

The mechanism of the increased nitrogen excretion has been in doubt. Bateman (6) suggests that tetracycline causes increased tissue catabolism, while Gabuzda (3) feels that tetracycline inhibits a riboflavin-dependent enzyme system which is necessary for the maintenance or synthesis of tissue protein. More specifically, Gabuzda believes that tetracycline inhibits the complexing of soluble ribonucleic acid to amino acids to form microsomal ribonucleoproteins. Falloon noted that with tetracycline administration the urinary riboflavin increased proportionately to the urine nitrogen (4). Gabuzda found that with tetracycline administration the rise in urinary riboflavin excretion preceded the increased nitrogen excretion (3). Enslie-Smith noted that in acute tubular necrosis due to poisoning or circulatory disturbances there is evidence of proximal tubular dysfunction manifested by diminished para-amino-hippuric acid clearance, glycosuria and amino-aciduria (7). Shils found that following tetracycline administration, a negative nitrogen balance developed but that the potassium balance did not follow a negative course (8). Because of the dissociation between nitrogen and potassium balances, he believes that tetracycline must have an anti-anabolic rather than a catabolic effect.

The most recent elucidation of the toxicity of tetracycline has been by Frimpter *et al.* who noted the development of a Fanconi-like syndrome in three patients following tetracycline administration (2). In all cases they analyzed the in-

gested drug and found variable quantities of both anhydro-tetracycline and epi-anhydro-tetracycline. They state that it is contamination of tetracycline by these degradation products which is responsible for the nephrotoxicity and other metabolic effects of tetracycline.

Our patient ingested outdated tetracycline and developed persistent glycosuria in the presence of normal blood sugars, a metabolic acidosis with hypokalemia and hyperchloremia. In addition she produced an alkaline urine with fixed, low specific gravity. Hypophosphatemia was present, indicating defective reabsorption of phosphate. These are manifestations of renal tubular dysfunction. Whether or not toxic degradation products of tetracycline were present was not determined.

SUMMARY

A 31 year old white female without prior renal disease developed signs and symptoms of nephrotoxicity, nausea, vomiting, profound dehydration and acidosis following ingestion of outdated tetracycline. Complete recovery ensued over a four-week period. A review of some of the metabolic effects of tetracycline is included.

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The Management of Patients with "Papilledema"

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When an individual presents evidence of "papilledema," the immediate reaction of the physician is usually one of grave concern, since a brain tumor is considered likely in spite of many other etiological possibilities. Most of the patients described in this paper initially consulted an ophthalmologist. Subsequently, they were referred to a neurosurgeon—rarely to a neurologist. They are being reported here because mass lesions have not been proved in these cases and important changes have recently been made in the neurologic diagnostic investigation.

The patients seem to be in two categories. One group consists of patients who have ophthalmoscopic evidence of blurring of the optic discs with or without retinal hemorrhage, and lumbar puncture confirms the presence of increased intracranial pressure. The other are patients in which the optic discs appeared to indicate papilledema, but there was no increased intracranial pressure and they were subsequently discharged with the diagnosis of pseudopapilledema.

Case 1. An 11 year old girl had a two-week history of nausea and vomiting associated with headaches. The headaches were progressive and became severe enough to require a visit to her physician who noted papilledema and recommended hospitalization. On the day prior to admission, she complained of double vision. The general examination was normal. The neurologic examination revealed fundoscopic evidence of bilateral papilledema with hemorrhages present in the right eye, a fine horizontal nystagmus on lateral and upward gaze, and double vision at approximately twenty inches away from the eyes. (It was thought by some that she had a convergent squint and by others that there was a left lateral rectus paresis.) Although visual acuity was normal, the visual fields revealed abnormally large blind spots. An electroencephalogram report stated "posterior slowing, compatible with a posterior fossa tumor and internal hydrocephalus." The remaining clinical laboratory tests, including skull x-rays, were normal. A lumbar puncture was not performed because of objections by the neurosurgical service. A ventriculogram revealed a normal ventricular system without any evidence of a mass lesion. Nevertheless, because of the increased intracranial pressure, it was decided to do a right subtemporal decompression. Eight years later, the patient was asymptomatic, her decompression was soft, ophthalmoscopic examination revealed mild optic atrophy. Her nystagmus was still present and, at this time, was considered to be most likely on a congenital basis.

Case 2. A 43 year old woman was hospitalized because of blurred vision for one month. Two weeks prior to admission, she developed black spots in the right upper visual field. This was followed by one episode of diplopia. She had had headaches as long as she could remember, but they became worse during the present illness. The clinical examination was entirely normal, except for both fundi, which showed bilateral papilledema with hemorrhages. The blind spots were enlarged. Other than lumbar puncture, clinical laboratory data, including electroencephalogram and skull x-rays, were normal. The first spinal tap revealed clear, colorless fluid, initial pressure of 380 mm of fluid, four lymphocytes, and protein 27 mg%. She was observed on the neurological service for eight weeks, during which time she had three additional lumbar punctures. All demonstrated high spinal fluid pressures, the highest being

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over 500 mm of fluid. The blind spots remained enlarged and visual acuity remained normal. To clarify the diagnosis, the neurological service recommended a pneumoencephalogram. Because the neurosurgical service feared this procedure under these circumstances, cranial burr holes prior to the lumbar puncture were agreed upon. The patient underwent the operative procedure, but ventriculography was done instead of a pneumoencephalography. No mass was noted. However, the posterior fossa area was not well visualized and an exploration was performed which revealed no pathology. The aqueduct was probed with a catheter and no obstruction was noted. She had a relatively stormy postoperative course, but eventually did well and was discharged with the diagnosis—papilledema, cause unknown. When she was last seen in the follow-up clinic eight years later, she was asymptomatic and the fundoscopic examination, which was normal four months after discharge, was still normal.

Case 3. A 14 year old boy was hospitalized with a six-year history of generalized headache. He had mild head pains, but five days prior to admission, he awoke with a severe generalized throbbing headache. He was sent home from school because the pain interfered with class-work. There were no other neurological symptoms. He was seen by his physician, who advised immediate hospitalization because of ophthalmoscopic evidence of papilledema, including tiny radial hemorrhages of both optic discs. The neurologic examination was otherwise normal, as was the clinical laboratory work-up, including skull x-rays, electroencephalograms and visual fields. A lumbar puncture revealed an initial pressure of 125 mm of fluid, and no cells were seen. Pneumoencephalogram revealed mild dilatation of ventricular system, but no evidence of a mass. He was discharged with the diagnosis of papilledema, cause unknown. Follow-up nine years later revealed he admitted to still having occasional headaches. There was no change in the optic discs, except that hemorrhages were not seen.

Case 4. An 8 year old girl developed frontal headaches two months prior to admission. A preschool checkup revealed evidence of papilledema and hospitalization was advised. The neurological examination was entirely normal. (There was a difference of opinion among the attending neurologists as to whether papilledema was present or not.) An ophthalmologist was suspicious of papilledema but stated that she should be observed further. Visual fields, including blind spots, skull x-rays and electroencephalograms, as well as the routine laboratory tests, were normal. A lumbar puncture revealed initial pressure 120 mm fluid, no cells and normal protein. She was discharged without a pneumoencephalogram and the diagnosis of pseudopapilledema. A three year follow-up revealed no signs or symptoms of intracranial disease.

Case 5. A 10½ year old girl was hospitalized for a pneumoencephalogram. Four weeks prior to admission, she developed intermittent stinging and burning of both eyes, lasting about thirty minutes. An ophthalmologic examination revealed evidence of papilledema. Visual fields, including blind spots, were normal, as were the skull x-rays and electroencephalograms. A neurosurgeon recommended craniotomy and she was listed for admission to another hospital. A neurologist was then consulted who thought she should be watched since there were only minimal clinical signs and symptoms. During the next fourteen days, there were no changes in the patient's clinical state and hospitalization was not thought necessary, but the parents had been so frightened by the diagnosis of possible brain tumor that they insisted upon a more definitive study. On admission, the neurological examination was normal, except for blurred optic discs and a fine nystagmus on lateral gaze, which was considered due to phenobarbital administration. Repeat visual fields, including blind spots, were normal. A pneumoencephalogram was normal (at that time, no initial manometric pressure was taken). Spinal fluid protein was 20 mg% and there were no cells. She was discharged with the diagnosis of pseudopapilledema.

These cases indicate some of the difficulties in diagnosis and management. A major problem is that one never knows beforehand whether a space-occupy-

ing lesion is present or not. The question is frequently raised: "The patient may have a mass causing increased intracranial pressure. Won't the lumbar puncture be dangerous in this situation?"

The majority of neurosurgeons believe that patients with presumptive evidence of increased intracranial pressure should have ventriculography, *i.e.*, cranial burr holes and air injected by a needle inserted through the cerebrum into a ventricle. The neurological opinion has been revised in recent years. This was stimulated by the unwillingness of neurologists to accept the dictum: "A lumbar puncture is dangerous in the presence of papilledema." This warning was first postulated by Cushing (1): "One recognized characteristic of a brain under pressure is its tendency to herniate through a cranial defect, and as there is normally an opening of the foramen magnum, a certain degree of protrusion is usually present there. In the presence of such conditions, the withdrawal of the cerebrospinal fluid from the meninges by lumbar puncture is often hazardous, as it may tend to a sudden wedging of the bulb in the opening, with anemia and paralysis of the vital centers." A series of 87 hospital admissions with papilledema was recently reviewed (2). A total of 75 lumbar punctures and 6 pneumoencephalograms were performed on 56 patients. Known pathology included subarachnoid hemorrhage, lead poisoning, torulosis and 38 neoplasms, 7 of which were in the posterior fossa. In no case did lumbar puncture or pneumoencephalogram significantly alter the clinical course. Actually, in 1929, Masson (3) reviewed 200 similar cases and, in 1933, Schaller (4) investigated 103 cases with papilledema and arrived at similar conclusions as to the lack of morbidity following the spinal tap. In textbooks, it is stated that lumbar puncture may be done in the patient with papilledema, but with extra care and under special circumstances; nevertheless, the fear of this procedure under these circumstances is quite evident. In 1949, Lindgren reported pneumoencephalography with the removal of less cerebrospinal fluid than air injected and concluded that reactions such as headaches, nausea, vomiting, syncope were much diminished (5). Since then, David, Ruggiero and Talairach discussed pneumoencephalography in 40 cases of brain tumors, 25 of whom had papilledema, and the sequelae of the procedure were minimal (6). Cravioto, Korein and Villanova reported 100 cases in which a pneumoencephalogram was performed and with the removal of a minimal amount of fluid (7). Their series included 21 brain tumor suspects, including 5 cases of papilledema. Again, no untoward effect was noted.

As a result of the above studies, it is thought that papilledema is not per se a contra-indication to lumbar puncture and, actually, in selected cases, a pneumoencephalogram can be performed.

The following cases demonstrate the changing management of these patients.

Case 6. A 28 year old woman was admitted with a chief complaint of headaches for three weeks and double vision for two weeks. Prior to hospitalization, there was a gradual onset of left frontal headaches. A week later, she noted double vision and had to cover her left eye in order to see clearly. Neurological examination was normal, except for bilateral papilledema, with a few splinter hemorrhages and exudates near the disc margins of both eyes. There was a left external rectus palsy. Blood studies and urinalysis were normal, as were skull x-rays and

an electroencephalogram. The visual fields showed some increase in blind spots bilaterally. The lumbar puncture revealed clear, colorless fluid, under a pressure of 150 mm of fluid. There were three lymphocytes and the protein was 25 mg%. The patient had bilateral burr holes inserted on the fifth day of admission. She then had a pneumoencephalogram, which was normal. An angiogram was performed to establish whether the patient had a venous thrombosis. This, too, was normal. There was an uneventful hospital course, both symptoms and papilledema regressed. One year later, she had slight weakness of the left external rectus muscle and normal optic discs.

Case 7. A 23 year old woman was admitted with the chief complaint of double vision of thirty-six hours duration. She was well until seven days before admission, when she struck her right temple after she slipped on a wet spot on the floor. She was not rendered unconscious. Two days prior to admission, she awoke and had difficulty focusing her eyes, especially on looking to the left side. She began to notice double vision at a distance, especially on left lateral gaze. A neurological examination was normal, except for bilateral papilledema, with many small, flame-shaped hemorrhages and exudates. There was diplopia on left lateral gaze. Blood studies, urinalysis, and skull x-rays were normal. An electroencephalogram revealed a minimal abnormality consisting of slight posterior slowing. There was bilateral enlargement of the blind spots and slight constriction of the entire right visual field. The first lumbar puncture showed an initial pressure of 50 mm, no cells and a 20 mg% protein. She had a pneumoencephalogram without any previous burr holes and this was normal. She was discharged fourteen days after admission, asymptomatic with almost normal discs.

Case 8. A 45 year old woman was admitted because of intermittent headaches for five weeks. There was spontaneous onset of a mild headache five weeks prior to admission and this was followed by objective vertigo with nausea, usually occurring when bending over. The attacks of vertigo occurred two to three times a day and lasted as long as ten minutes. She also complained of seeing double, objects either being side by side or one above another. Also, the objects constantly changed in shape and position. She occasionally noted spots flashing past her left eye. Her visual acuity had become somewhat impaired, so that she could no longer read newspapers. The neurological examination was entirely normal, except for impaired visual acuity, bilateral severe papilledema with hemorrhages. In addition, she could not tandem walk, but there were no other cerebellar findings. Blood studies, urinalysis, electroencephalogram, and skull x-rays were normal. The visual fields were normal, except for enlarged blind spots. A lumbar puncture revealed initial pressure of 330 mm, and the protein was 10 mg%; two lymphocytes were noted. A pneumoencephalogram was normal. She did well following the procedure and was treated by low salt diet, Diamox, and repeated lumbar punctures. She was discharged, improved, sixteen days after admission, but re-admitted one month later, because of a chief complaint of swelling of the fingers and legs. An extensive medical work-up did not reveal any diagnosis. Her optic disc had become normal and there were no visual symptoms. A lumbar puncture was performed at this time and the initial pressure was 70 mm of fluid.

Case 9. A 15 year old boy was admitted with a four-week history of headache and a two-week history of double vision, occurring mainly in the lateral plane. He stated that the images became further apart when he looked at a distance. The neurological examination was normal, except for bilateral blurred discs, the right being more involved than the left. During the first three hospital days, transient nystagmus was noted on right lateral gaze, as well as weakness of the right external rectus muscle. Hemoglobin, white cell count, sedimentation rate, blood sugar, protein, cholesterol, calcium and phosphorus were normal; the urea-nitrogen was 23 mg%. A repeat blood sample was 22 mg% and the uric acid at that time was 6.9 mg%. This, too, remained elevated upon further sampling. Repeated urine examinations were always normal. Skull x-rays, electroencephalogram were normal, as was the cold caloric examination. There were enlarged blind spots. A lumbar puncture revealed clear, colorless fluid and pres-

sure of 270 mm of fluid. No lymphocytes were seen. The total protein was 16 mg%. Pneumoencephalogram was attempted, but air did not enter the subarachnoid space or ventricular system. It was thought that the needle was in the subdural space rather than in the subarachnoid space. Permission to repeat the study was denied. He was discharged one week later, for he clinically improved. A four year follow-up revealed no symptoms, although blurring was still present in the right optic disc.

In the patients herein described, one outstanding observation is that all these patients were in excellent physical condition. Neurological symptoms were minimal, consisting of headaches and diplopia, with occasional impairment of visual acuity. Neurological findings were mainly limited to the ophthalmoscopic evidence of what appeared to be papilledema, occasional nystagmus and external rectus palsy. The patients with pseudopapilledema were usually younger people, who either had mild symptomatology or were seen in routine examination, at which time an abnormality of the retina was noted. The older patients with true papilledema were also not in any acute distress, but suffered from headaches and, at times, diplopia. There are many conditions which cause papilledema or retinal changes simulating choked disc, such as retrobulbar optic neuritis, occlusion of retinal veins, diabetic retinopathy, syphilitic papillitis, uremia, hypoparathyroidism, meningitis, chronic pulmonary insufficiency and otitis media. The latter condition, also known as otitic hydrocephalus and pseudotumor cerebri, is usually considered under the category of intracranial hypertension of unknown etiology (8). Naturally, this diagnosis is a retrospective one, after all other known possibilities have been eliminated. The etiology of this condition is still unknown, although it is thought, especially when an otitis media is present, that there may be a thrombosis of the lateral sinus and, in postpartum states, a theory has been postulated of embolization originating in a pelvic vein, passing through the pelvic vertebral plexus to the superior sagittal sinus. Actually, there is no definite knowledge as to the cause of the benign form of increased intracranial pressure. Of major importance is the knowledge that the prognosis in this condition is relatively good. Many patients are treated by low salt diet and diuretics; occasionally, repeat lumbar punctures have been efficacious and, only rarely, do such patients require craniotomy. As noted, ventriculography was performed in some of the cases reported in this series. Inserting a needle through the brain to reach the ventricle is not a benign procedure (9). Severe complications are reported (10) and, if possible, the procedure should be avoided.

Inasmuch as patients with neoplasms and papilledema have been investigated by lumbar puncture and "fractional" pneumoencephalography without ill effects, the point to be emphasized is that papilledema does not necessarily mean a patient must go to surgery for ventriculography and possible subtemporal decompression. The important factors are the patients' relatively excellent clinical condition and the paucity of neurological findings. It is good neurological judgment to be wary of doing diagnostic procedures in critically ill patients, who demonstrate obvious neurologic defects. The management of such patients is very difficult. However, in the group of patients described above, surgical diagnostic procedures may be harmful or, at the very least, may be unnecessary.

CONCLUSION

Patients who present with papilledema and minimal neurological findings do not necessarily have space-occupying lesions.

Such patients may be investigated neurologically, including lumbar puncture and "fractional" pneumoencephalography. Consequently, intracranial surgery may be avoided.

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CLINICO-PATHOLOGICAL CONFERENCE

Acute Abdominal Pain, Bloody Diarrhea and Anuria

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A four year old white female child was transferred to The Mount Sinai Hospital from a New Jersey hospital where she had been anuric for 48 hours. Her illness began 15 days earlier with sudden sharp midepigastria pain and progressively loose diarrheal stools with dark red blood. She was treated initially with erythromycin, paragoric and Kaopectate. Her symptoms, however, became more severe, with nausea, vomiting, anorexia and fever. Two days later a mass was felt in the right lower quadrant. Rectal examination disclosed "currant jelly" stool. On this basis a diagnosis of intussusception was made, and the patient was hospitalized. A laparotomy revealed "regional colitis" extending from the mid-transverse colon to the splenic flexure. The bowel wall was described as thickened, and the mesentery showed "bullous emphysema" and mesenteric adenitis. An appendectomy and a lymph node biopsy were performed. The pathological report was lymphoid hyperplasia of the appendix and hyperplastic lymph node.

Postoperatively the patient vomited daily and her urine output decreased progressively, *e.g.*, 630 ml, 500 ml and 300 ml in the first three postoperative days. On the first day 2,500 ml of dextrose/water had been given. Oral fluids were permitted thereafter. On the second postoperative day, her temperature rose to 101°F and Terramycin therapy was begun. By the sixth postoperative day, the marked leukocytosis found on admission had improved. The patient's hemoglobin had fallen from 12.4 Gm% to 7.2 Gm%. She was given a transfusion of 300 ml of whole blood without sequelae. On the eleventh postoperative day, the patient had been anuric for 24 hours. Her bladder was not distended. She received 1,000 ml of 5% dextrose in water and 200 ml of whole blood. On the same day, edema of her face and hands was noted for the first time, and a provisional diagnosis of "nephritis" was made. On the twelfth postoperative day, she was transferred to The Mount Sinai Hospital.

Physical examination here disclosed a toxic, semi-comatose, pale and frankly edematous child with ecchymoses of both antecubital fossae. Her temperature was 101°F, pulse (radial) 36/min., ventricular rate 120/min. and irregular with premature ventricular contractions, blood pressure 90/50. Her face and eyelids were edematous. The fundi were normal. Blood was noted in the hypopharynx. The neck was supple, with distended veins filling from above. The lungs were clear. The rhythm of the heart was grossly irregular. The point of maximal impulse was in the midclavicular line in the fifth interspace. A systolic gallop was heard but there were no murmurs or thrills. The liver edge was felt two finger-

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breadths below the right costal margin and the spleen was not felt. No peripheral adenopathy was found. Both upper and lower extremities were puffy but did not pit on pressure. Reflexes were not obtainable.

Laboratory studies are in Table I. An electrocardiogram showed multiple premature ventricular contractions, tall peaked T-waves and questionable ventricular tachycardia. Bedside films of the chest and abdomen were poor technically but no abnormalities were noted. A blood culture was negative. The urine culture was overgrown with *B. proteus*. Stool cultures, febrile agglutinins and a Coombs' test were negative. No abnormal cells were seen on blood smear, which showed only a left shift, some achroma, macrocytosis and microcytosis.

The patient was started on small amounts of intravenous fluids with 2,000,000

TABLE I
Laboratory Data

	Referring Hospital			The Mount Sinai Hospital
	Day of Operation	6th P.C. Day	11th P.O. Day	12th P.O. Day
Urine				
Spec. grav.	1.032			1.014
Albumin	tr			4+
WBC/hpf	4-6			4-6
RBC/hpf	1-2			6-8
Casts	occ. hyalin and granular			many hyalin and granular
Hemoglobin Gm%	12.4	7.2	12.0	10.8
RBC/mm ³	5,500,000	2,510,000	3,940,000	
WBC/mm ³	44,150	13,250	11,800	13,900
BUN mg%			84	139
Potassium mEq/L			8.4	7.9
Sodium mEq/L			132	115
CO ₂ mEq/L			22	6.7

units of penicillin per day. Schumm's test for methemalbumin was negative as was examination of a blood smear and search for hemosiderin in the urine.

Before further therapy or diagnostic procedures could be attempted, the patient expired nine hours after admission.

*Dr. Donald Gribetz**: This four year old girl presented with what appeared to be an acute abdominal episode accompanied by diarrhea; this ultimately was followed by acute renal failure. I thought it would be best to analyze first the possible causes of the initial gastrointestinal episode.

The initial question that arises is one of surgical intestinal emergencies. In the first hospital intussusception was thought to be a leading possibility. The thickened bowel wall could have been the result of a reduced intussusception. The fact that there was diarrhea instead of the usual constipation does not rule

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against intussusception. A second surgical condition that could cause such an onset is a Meckel's diverticulum in a child. This usually appears with massive bleeding per rectum. A third condition that has to be considered from the point of view of the surgical emergencies is a peptic ulcer with bleeding. It is relatively rare at this age and there was no antecedent history of gastrointestinal complaints. Another possibility is midgut volvulus secondary to a malrotation. This, too, could present with a sudden onset of pain and bloody diarrhea. However, there is no evidence of acute intestinal obstruction such as a distended abdomen, bile-stained vomitus which probably should have occurred after 48 hours, or any constipation. In addition, at surgery, the finding which hints at malrotation was not mentioned, *i.e.*, the cecum was not described as being out of its usual locus in the right lower quadrant.

A factor in the protocol that makes me worry if we have completely ruled out the surgical emergencies is the question of bullous emphysema which was found in the mesentery.

There is a condition that has been described in children called pneumatosis intestinalis. Cysts are found either in the mesentery or in the wall of the gut, and these are thought to be nonspecific findings associated with intestinal obstruction or some congenital anomaly of the gastrointestinal tract. The mechanism is postulated to be air leaking through the damaged gut wall to the surrounding tissue. I hesitate to dismiss the bullous emphysema completely and I would have to keep in mind that perhaps the child did have some acute abdominal emergency which was not found at operation, such as an intussusception which may have rectified itself.

In addition to the acute surgical condition, two other gastrointestinal problems come to mind which could have presented in the described fashion in a child, *i.e.*, ulcerative colitis and regional ileitis. Their usual onset is not with severe epigastric pain and sudden bloody diarrhea but both are possibilities.

Another class of problems that could present this way is obviously the acute intestinal infections such as those caused by either *Salmonella* or *Shigella* organisms. Two or three others also come to mind, such as cholera, leptospirosis and, as recently emphasized in pediatric literature, viral epidemic hemorrhagic fever. These could also be associated with acute renal failure.

The next large group of conditions which has to be considered is that of poisoning or drug intoxication. There are several drugs and poisons that could present exactly this way. An overdose of iron salts, mercury or arsenic poisoning, or ingestion of insecticides or rat poisons which contain warfarin, the anticoagulant, can certainly cause this kind of an onset. There has been no mention of any ingestion of poisons and drugs like these nor has there been any comment that the child was previously ill.

Blood dyscrasias must now be seriously evaluated. Idiopathic thrombocytopenia comes to mind first as a possibility. There is one very basic piece of information that is not available, however, and that is the platelet count. The child had no purpura except for "ecchymoses of both antecubital fossae" which prob-

ably resulted from the numerous venipunctures that she must have had. Also, there was no preceding upper respiratory infection mentioned nor any preceding exanthematous disease such as chickenpox or rubella, conditions which sometime precede thrombocytopenic purpura in a child of this age.

Another possibility is non-thrombopenic purpura. We in pediatrics occasionally see this condition appear with an acute onset of abdominal pain and melena prior to ecchymoses and petechiae and sometimes without any of the usual urinary findings. This is a distinct possibility and, in fact, may be linked to one of the surgical possibilities mentioned, namely, intussusception. There is apparently an increased incidence of intussusception in Henoch-Schönlein non-thrombocytopenic purpura. I would presume, though, that after thirteen days, if this really was the case, that there would have been more of the cutaneous manifestations of the purpura.

Acute hemolytic episodes occurring in the midst of diseases such as spherocytosis, Cooley's anemia or sickle cell anemia could cause this onset but there is no evidence that the child was ill previously. These diseases are usually more chronic, with onset earlier in life and are associated with splenomegaly.

To account for an acquired hemolytic anemia, the striking fall of the hemoglobin from 12 Gm% to about 7 Gm% within five to six days after the operation with no indication that the child continued to bleed would have to be explained. Here another bit of information is missing, *i.e.*, a detailed description of the blood smear. There was some microcytosis and macrocytosis, but no mention is made about bizarre forms, reticulocytes, nucleated red cells or other evidence of hemolysis. There were no drugs mentioned that could be implicated for hemolysis. There are no data concerning autohemagglutinins or autohemolysins, and there is no evidence that the child might have had a coexisting collagen disease like lupus or periarteritis which could have been associated with a hemolytic anemia. We can, nevertheless, attempt to link the two situations: the acute abdominal episode with the diarrhea plus the progressive renal failure ending with anuria.

If we assume that the acute abdominal emergency was intussusception, Meckel's diverticulum or one of the others mentioned, it would then be incumbent upon us to explain why oliguria and finally anuria developed from what would have appeared to be a routine surgical procedure. No information is available that during the operation there was a fall in blood pressure which could have led to acute renal failure. There is also no history of a period of dehydration postoperatively since on the very first day 2,500 ml of dextrose/water were given and oral fluids were permitted thereafter. We would assume, therefore, that the child was tolerating fluids and never became dehydrated. On the contrary, I think one of the problems was that this child was overhydrated. Acute anuria and renal failure postoperatively can be caused by the promiscuous use of morphine or Demerol® which has been shown to have an antidiuretic effect in certain children. There is no mention of this, and one would assume that this did not happen.

The question of the relationship of the transfusion to the renal failure must be raised. The transfusion was given on the sixth postoperative day, and the

suggestion is that the child was becoming oliguric before that time. I therefore would hesitate to incriminate a transfusion reaction.

If we attempt to link the two episodes with various bacterial infections, a distinct relationship could be made. Endotoxins and other toxic products of *Salmonella*, *E. coli* and *Shigella* can "travel" through the bloodstream to the kidney and cause some form of renal damage, usually cortical necrosis. Several years ago we had a child on our pediatric service who apparently had an acute *Salmonella* infection and died with bilateral cortical necrosis. This has to be strongly considered as the diagnosis.

I would prefer, however, to put the present case into another class of diseases which have been reported now with increasing frequency in the pediatric literature: the "hemolytic-uremic" syndrome. I am not certain whether this is a single disease or a group of diseases, nor am I sure about the etiology. This syndrome apparently is analogous to thrombotic thrombocytopenic purpura or Moschcowitz's disease in adults. Two rather important facts are missing from the protocol, however: 1) distinct thrombocytopenia, and 2) evidence that the cause of the fall of hemoglobin was actually hemolysis. As to the latter, there was no continuing blood loss nor any evidence of a deficiency of blood production. Furthermore, the amount of dilution that occurred in terms of the fluids that were given does not seem to be enough to account for the lowered hemoglobin. Therefore I am assuming, perhaps riskily, that this child may fall into the class of diseases which has been described as the "hemolytic-uremic" syndrome.

Most of the children with this syndrome are under one year of age and many had a low platelet count. There are central nervous symptoms like convulsions or delirium in about fifty per cent of this group but there is no hint of it in this child. There is a great deal of speculation as to what this disease syndrome is. Some claim it is a viral disease. Others feel that it is bacterial and that it may be due to *E. coli*. About half of the children who died from this condition have had bilateral cortical necrosis as the autopsy finding. Several have had findings compatible with acute glomerulonephritis and some have had the full-blown picture with thrombi in the capillaries throughout the body. I would expect, if the child does fall into this category, that we would find generalized thrombotic phenomena in many organs or that findings would be limited to the kidney with bilateral cortical necrosis or acute glomerulonephritis.

*Dr. Horace L. Hodes**: Dr. Gribetz said that the hemoglobin fall could not be accounted for by loss of blood at the operation or by hemodilution, but I would like to point out that a combination of these two factors might very well have given a hemoglobin of 7 Gm.

Dr. Gribetz, do you find fragmented red cells in the peripheral blood in the syndrome that you were discussing, as you would find in the adult?

Dr. Gribetz: They are fragmented and bizarre in shape. I do not think we have ever had a child on our service whom we recognized as having this disease. Burr cells and triangular shaped cells have been described. Dr. Rausen is on the program and I assume he is going to discuss the hematologic aspects.

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*Dr. Lotte Strauss**: Would it be easy, on a routine examination of the blood smear, to recognize these abnormal red cells?

Dr. Aaron R. Rausen†: I think that in poor blood smears, you may see things that look very much like burr cells so that it has to be an adequate blood smear. Technicians are aware of these cells and then the diagnosis can be made immediately.

Dr. Strauss: The body was that of a well-developed white girl of four years. The skin was pale and showed neither icterus nor purpura. In the regions of the ankles, knees and sacrum there was 1+ pitting edema. The peritoneal cavity contained a few cubic centimeters of colorless clear fluid. A few adhesions were



FIG. 1. Circumscribed area of serosal hyperemia involving mid-third of large intestine (near splenic flexure).

found between the recent surgical scar and loops of terminal ileum. The appendix was absent. Injection of the serosa of the colon in the region of the splenic flexure was noted (Fig. 1). The pericardial cavity contained some xanthochromic fluid but no exudate or fibrin was observed. The urinary bladder was contracted and empty; petechiae were seen in the trigone. The kidneys were symmetrically enlarged, each weighing 80 Gm (expected weight 58 Gm), and had a smooth surface which was studded with pinpoint hemorrhages (Fig. 2). The cortex was swollen and on the cut surface showed similar hemorrhages. No infarcts were noted. The pyramids were congested and showed hemorrhagic streaking. There were no abnormalities of the calices, pelves and ureters.

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Histological examination of the kidneys revealed a severe bilateral lesion involving glomeruli and tubules. The glomeruli varied in appearance, some being almost bloodless, while others showed the most extreme dilatation and engorgement of the glomerular capillaries (Fig. 3). The basement membranes of the ischemic glomeruli were intact but the endothelial cells appeared swollen. Epithelial cells occasionally contained PAS-positive droplets. A considerable amount of sudanophilic material could be demonstrated in many glomeruli. Frequently the stalk vessel as well as some of the glomerular capillaries contained fibrin thrombi (Fig. 4). In places the capillary basement membrane was stained indistinctly and there was necrosis of part or all of the glomerulus, associated with hemorrhage and leukocytic infiltration. Only occasionally did afferent arterioles

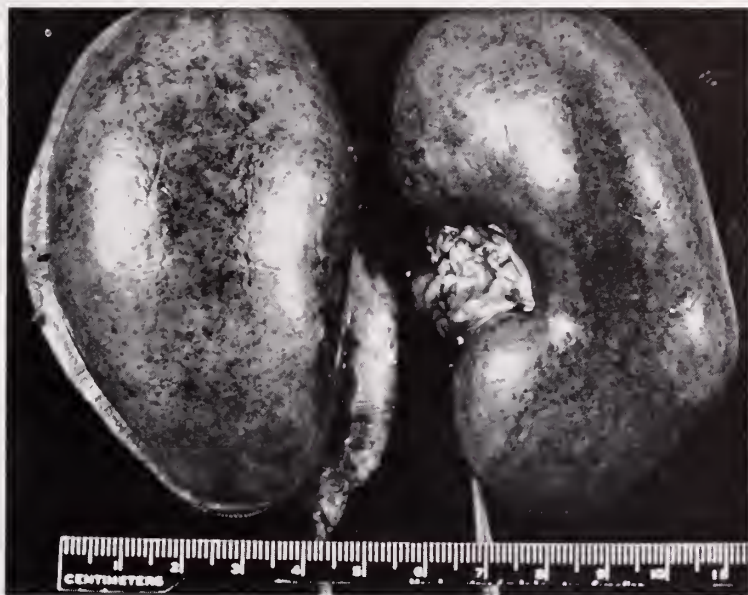


Fig. 2. Enlarged kidneys with multiple patchy hemorrhages scattered over the surface.

show acute necrosis, with protein and red blood cells in the wall (Fig. 3). The proximal tubules showed widespread patchy infarct-like necrosis (Fig. 5). They contained casts consisting of protein and necrotic cells. Intact proximal convoluted tubules were dilated, probably a compensatory phenomenon. Hyalin and fat droplets were present in many tubules. The distal tubules were for the most part intact, except for occasional focal necrosis as seen in shock. Marked venous stasis and focal hemorrhages were found in the medulla, but no venous thromboses. Except for the occasionally seen necrosis of afferent arterioles, there were no arterial lesions. Hemoglobin casts were found in some of the tubules. In summary, this picture was that of confluent focal bilateral cortical necrosis of the kidneys in a relatively early stage. It was interpreted as the result of a severe circulatory disturbance of the kidneys, due to vascular insult, which was not limited to the kidneys. Extreme capillary dilatation was seen in the mucosa

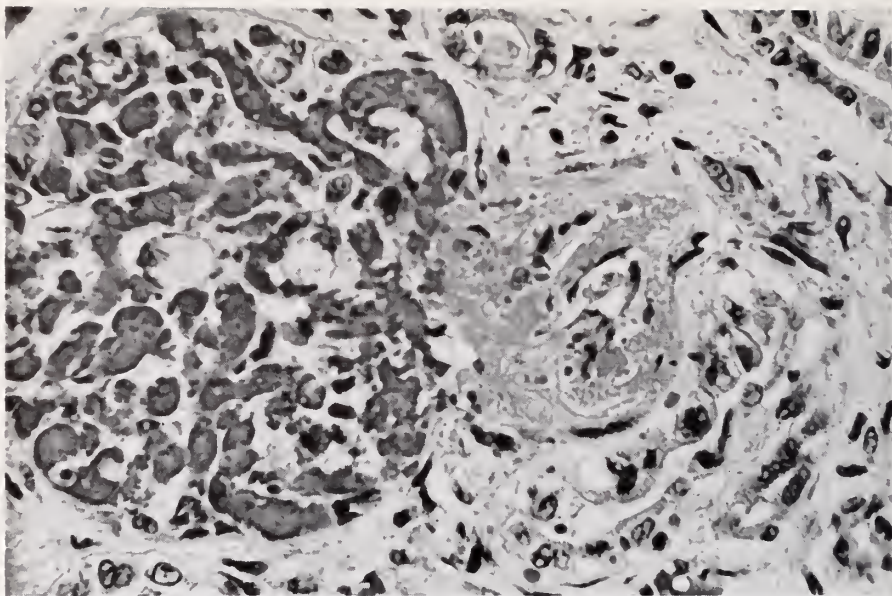


FIG. 3. Kidney: extreme dilatation of glomerular capillaries, and acute necrosis of afferent arteriole. (Hematoxylin and eosin, $\times 400$).

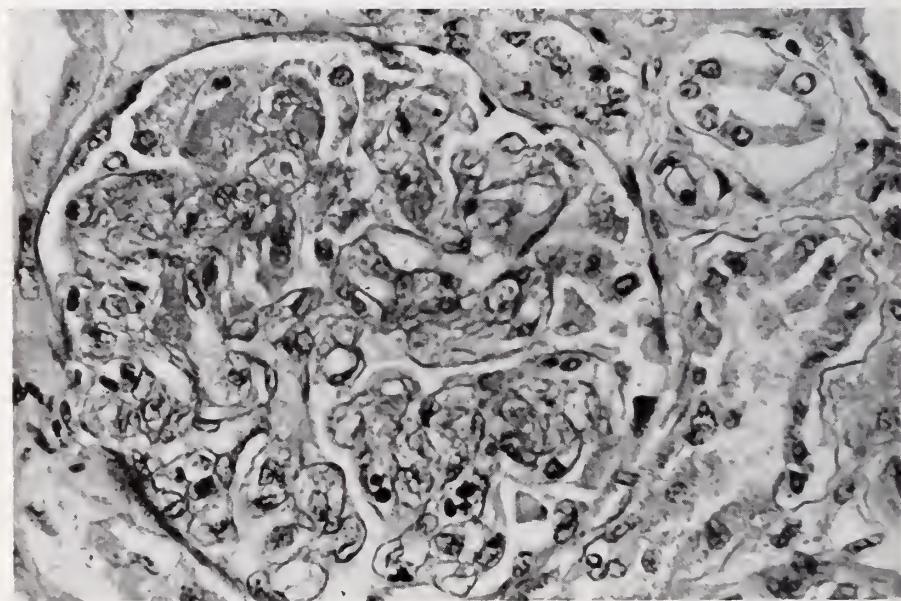


FIG. 4. Kidney: glomerulus with ischemic capillaries and several fibrin thrombi in glomerular capillaries. (Periodic acid-Schiff, $\times 400$)

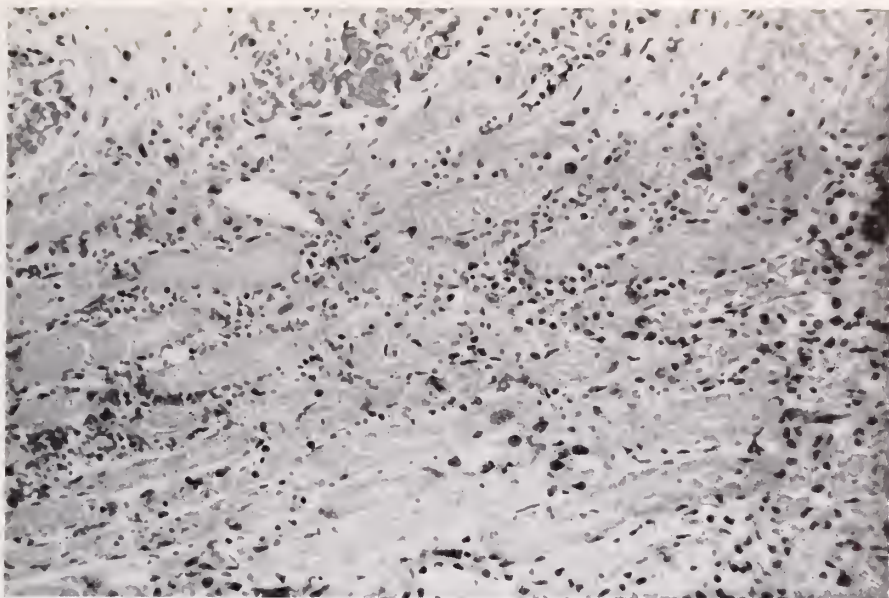


FIG. 5. Kidney: acute infarct-like necrosis of proximal convoluted tubules. (Hematoxylin and eosin, $\times 200$)

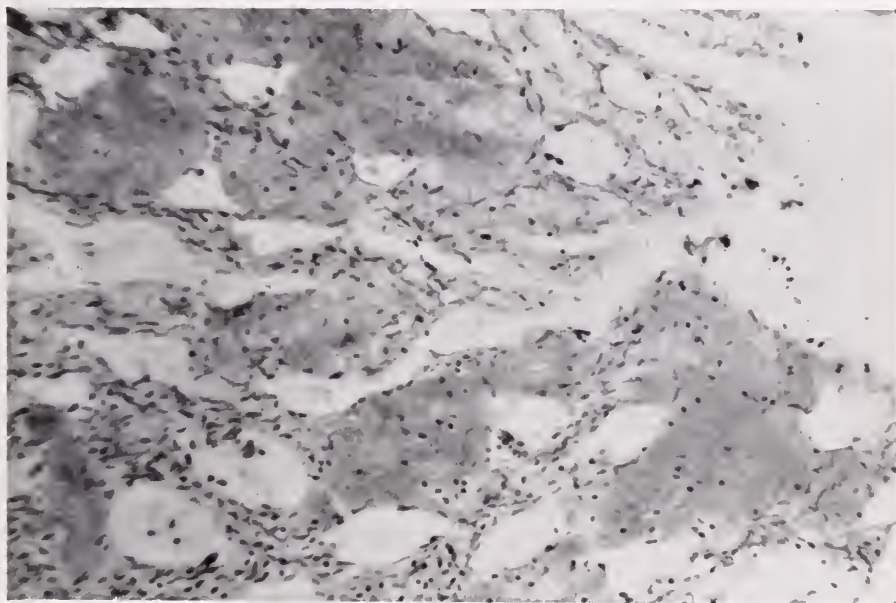


FIG. 6. Extreme vasodilatation in the duodenal mucosa. (Hematoxylin and eosin, $\times 200$)

of the duodenum (Fig. 6) and large intestine, and microscopic vascular injury was also observed in the wall of the colon (Fig. 7), and in the epicardium. This was, however, not the picture of necrotizing angiitis as seen in hypersensitivity states. Purpura was particularly striking in the myocardium, in the absence of visible vascular lesions. Unfortunately we do not know whether the patient had any defect in her blood clotting mechanism, and what her platelet count was.

Now we come to the anemia. The spleen was not significantly enlarged. However, it showed a striking active hyperemia as well as hemosiderosis. The Kupffer cells in the liver also were filled with hemosiderin. There was no

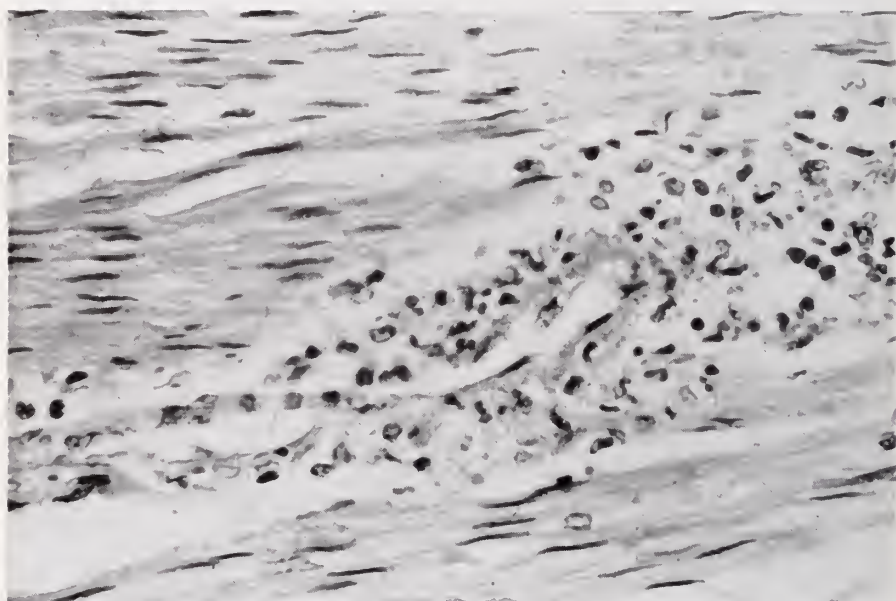


FIG. 7. Acute necrosis of small blood vessel in the wall of the transverse colon. (Hematoxylin and eosin, $\times 400$)

erythrophagocytosis. The bone marrow showed erythroid hyperplasia. These findings establish the presence of a hemolytic process. Intravascular hemolysis was suggested by finding of hemoglobin casts in the kidneys.

The liver was diffusely fatty and showed severe congestion and swelling of the Kupffer cells which contained PAS-positive material as well as iron pigment. There was no necrosis and no vascular lesions or fibrin thrombi. Those lymph nodes which were examined showed little reactive changes except for increased phagocytic activity in the germinal centers of the follicles.

There was moderate lipid depletion of the adrenal cortices.

The heart showed an acute nonspecific pericarditis (Fig. 8), without exudation of fibrin. No microorganisms were found on bacterial stains.

The pathological alterations which I have shown can be summarized briefly as resulting from a severe vascular insult, which, while generalized, finds its

most dramatic expression in bilateral renal cortical necrosis, an acute hemolytic process, and an acute nonspecific pericarditis of undetermined etiology. How are these findings related and what is their causation?

It is known that bilateral renal cortical necrosis occurs in man in certain more or less well-defined situations, the majority of the described cases being associated with pregnancy (Table II).

A syndrome of acquired non-immune hemolytic anemia with thrombopenia and nephropathy has been reported with increasing frequency in recent years, since the report of Gasser *et al.* who described the clinical and necropsy findings in five fatal cases (1). About sixty cases have been reported by now, the majority in infants under one year of age. However, it may occur in older children (1 to

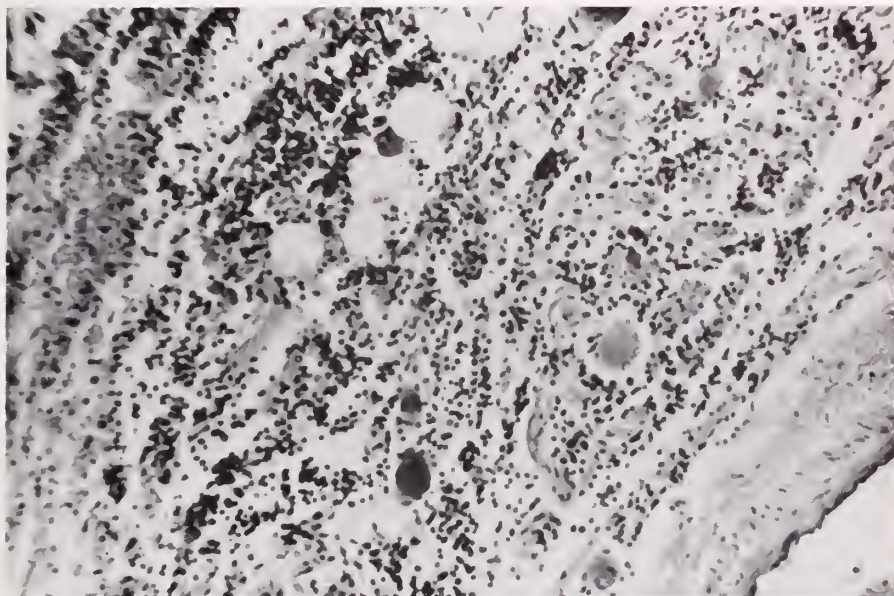


FIG. 8. Epicardium: acute nonspecific pericarditis. (Hematoxylin and eosin, $\times 200$)

3). About one-third of the reported cases have been fatal, and autopsy studies have revealed bilateral renal cortical necrosis or, in some cases, glomerulonephritis (4 to 6). One paper only reports platelet thrombi in the kidneys and other organs; for this reason the condition has been related to thrombotic thrombocytopenic purpura (7). The primary agent on which both hemolytic syndrome and the nephropathy are thought to depend is unknown. The onset of the illness with signs of respiratory tract or intestinal tract infection in many patients has suggested that bacterial toxins or the action of a virus may have etiological importance (1, 8, 9). Drug sensitivity has also been considered.

If recovery takes place it is usually complete in about one month after the onset of illness, although proteinuria and an elevated BUN may persist for some time. In the autopsied cases the renal lesion was almost invariably severe and probably accounted for the fatal outcome.

Bilateral renal cortical necrosis was first described in 1885 in a 16 year old girl with scarlet fever (10). Case reports in children have appeared in the literature since 1913. It is now widely accepted that the mechanism of renal cortical necrosis resides in ischemia produced by changes in the renal vasculature. The circulatory disturbance is not confined to the kidneys, and one can find evidence of vascular damage in other organs, especially in the digestive tract where they are usually designated as shock lesions. Such lesions have been produced experimentally by various substances of bacterial origin as well as by chemical poisons (11); they are probably mediated by the central nervous system.

The hemorrhagic colitis observed in our patient at laparotomy and still present at autopsy is similar in localization and histological characteristics to

TABLE II
Renal Cortical Necrosis

- I. *Pregnancy*
 - eclampsia
 - retroplacental hemorrhage
 - amniotic fluid embolism
 - septic abortion
- II. *Infections*
 - streptococcal, pneumococcal, diphtheria
 - malaria dysentery
 - coliform organisms (endotoxin)
- III. *Exogenous Toxins, Drugs*
- IV. *Shock*
 - of various causation
- V. *Syndrome of Hemolytic Anemia, Thrombopenia and Nephropathy*
 - mostly in infants, cause?
- VI. *Experimental*
 - staphylococcal toxin
 - gram-negative endotoxin ("general Schwartzman phenomenon")
 - serotonin

the experimental lesions described by Penner and Bernheim (12). It is possible that endotoxins appeared in the circulation following the intestinal lesion, thus precipitating the renal lesion.

One may thus reconstruct the sequence of events in our patient in the following way: The initiating insult is not known but may have been an infection, bacterial or viral (pericarditis?). An exogenous toxin or a dietary factor cannot be ruled out, especially in a young child. The hypothetical circulating toxin produced changes in the gastrointestinal tract, particularly the duodenum, cecum and midcolon, giving rise to blood-streaked diarrhea and abdominal pain. Subsequent events could be explained on the basis of endotoxemia, resulting in renal ischemia and cortical necrosis as seen in the generalized Schwartzman reaction. We have observed such a case in a three year old boy with *Salmonella* infection, and it is well known to occur in infants infected with pathogenic strains of *E. coli*. Whether the renal lesion must be secondary to an intestinal insult is moot since renal cortical necrosis has been produced experimentally with substances

other than bacterial endotoxin, such as staphylococcal toxin or serotonin. On the other hand, we remember that in this patient intestinal symptoms preceded the appearance of renal symptoms.

The role of surgical intervention in precipitating the catastrophic renal injury is problematic. Cases have been reported of acute renal failure following abdominal surgery, after a symptom-free interval of a week to ten days.

The hemolytic anemia in this patient was probably of non-immune origin (negative Coombs' test). I believe that it was due to the primary insult rather than secondary to renal failure with azotemia. Although we have no platelet count and no report of red cell fragmentation, I felt that the syndrome which we have presented closely resembles the so-called hemolytic uremic syndrome as first described by Gasser *et al.* (1).

Its relationship to the generalized Shwartzman reaction on the one hand and to thrombotic microangiopathy (Moschcowitz's disease) on the other remains to be elucidated.

Dr. Rausen: Burr cells or pyknoocytes or acanthocytes should have been seen on careful examination of the blood smear. This has been described in the children who were thought to have the syndrome somewhat akin to the adult form of thrombocytopenic purpura, namely, the hemolytic uremic syndrome. They have also been found fairly consistently in individuals whose blood urea nitrogen is over 70 to 75 mg% for any length of time. This is particularly true in the presence of microspherocytes. Burr cells usually stain a bit more intensely than the normal cells and are characterized by having several spiny projections. They have to be seen in areas with normal cells to ascertain that they are not the result of a faulty preparation. There are two non-azotemic conditions that are characterized by the presence of these abnormally contracted erythrocytes. One is almost solely in the newborn period associated with hemolytic anemia of variable severity. This is much more prone to occur in premature infants and seems to be self-limited. This condition, which is characterized by large numbers of these small cells, has been called infantile pyknoctosis and may very well be due to a transient enzymatic defect similar to the other types of disorders peculiar in the newborn period, such as hyperbilirubinemia, without any known causation aside from improper or faulty conditions in the liver for a short period of time.

The other condition which has recently been better delineated is retinitis pigmentosa atoxia with peculiar types of burr cells in the peripheral blood smear. This condition is a genetic homozygous recessive disorder characterized by lack of beta globulin in the serum. There may be an additional deficiency that may account for the contracted cells that are also seen in the adults with this condition without any overt evidence of a hemolytic anemia.

Urea and other metabolic products in association with azotemia do not *in vitro* seem to induce hemolysis in otherwise normal cells. Some as yet unknown factor that may be common to these three conditions may account for the unusual cells present in all.

Dr. Strauss: Dr. Rausen, do you think that the hemolytic anemia present in this child could have been secondary to renal insufficiency with azotemia?

Dr. Rausen: In most cases of acute or chronic renal insufficiency, the anemia takes a fairly long time to develop. It usually reaches its maximum in four to six weeks after the development of acute renal failure, and this child's illness had only a five or six day course before maximal anemia occurred. In addition, the child had a very hyperplastic marrow which is fairly uncommon in acute renal failure. This is apparently the reason that children or adults with acute renal failure develop progressive slow anemia, primarily because the marrow cannot compensate for a mild hemolytic defect. In this case there must have been a fairly brisk hemolytic process if we are going to try to account for the sudden drop in hemoglobin in the face of what seems to be a hyperfunctioning bone marrow.

Dr. Hans Popper:* This was a beautifully described picture and very well studied. I wonder why we do not see that more often. This was probably the result of an endotoxin in the sense of a generalized Shwartzman phenomenon. *E. coli* are commonly found organisms but what occurred here in this exceptional case to cause this reaction?

Dr. Hodes: Are we not seeing more of these in overwhelming gram negative sepsis?

Dr. Popper: No, it is not part of the picture of overwhelming gram negative sepsis.

Dr. Hodes: I think there is another mechanism involved in the cases that we have had and in the ones I have read about. Entry of the bacteria into the wall of the intestine might be the factor. Not only is endotoxin needed but also necrosis of some kind which begins locally. In other words, a local injury must precede the generalized one.

Dr. Strauss: The question is how the injury in the intestine is produced. This would be peculiar if it were on the basis of a generalized vascular injury. What interested me is that it can be produced simply by injecting the toxin locally, for instance, into the central nervous system.

Dr. Hodes: Can it be blocked in a high percentage of cases?

Dr. Strauss: Yes.

Dr. Hodes: My guess would be that there is a local injury necessary. This has been described not only with *E. coli* but with what appeared to be viral diarrhea. I think one of the elements in this is an intestinal injury, maybe on a vascular basis first. There is abdominal pain and then somebody operates on these children which may also contribute to the condition.

Dr. Popper: It would develop even if they were not operated upon.

Dr. Strauss: The significance of the surgery is, of course, very problematic. There have been a number of cases described in which patients, after an initial benign course postoperatively, eight or ten days later develop uremia, convulsions and bilateral cortical necrosis.

Dr. Hodes: What has been added to the concept is the hemolysis and this might have been present all the time. We have perhaps not been sophisticated enough to think about it. I dislike seeing a new name used but I guess there is no help for it.

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Dr. Strauss: This child, however, was not anemic when she first came in, certainly not severely so. There was an abrupt drop in hemoglobin.

Dr. Gribetz: In the pediatric literature this was first described under the name of the hemolytic uremic syndrome in 1955 by Gasser and his group in Switzerland. Since that time there have been many case reports with different names attached to it such as "hemolytic crises with nephropathy," "burr cell disease" or "red cell fragmentation syndrome."

Dr. Rausen: In trying to relate this to the thrombotic thrombocytopenic purpura in adults, the Rochester group recently observed that the renal lesions and characteristic findings of thrombocytopenic purpura may take time to develop. They cited two cases with intermittent uremia, thrombocytopenia and hemolytic anemia. On biopsy they did not show evidence of the thrombotic thrombocytopenic purpura but it progressively developed and became more characteristic over a period of years. They then speculated that the acute cases do not have to develop the same types of changes that occur in the more classic ones of thrombotic thrombocytopenic purpura.

Final Diagnosis: BILATERAL RENAL CORTICAL NECROSIS (HEMOLYTIC UREMIC SYNDROME).

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RADIOLOGICAL NOTES

CLAUDE BLOCH, M.D., AND HARVEY M. PECK, M.D., *Co-Editors*

Pediatric Radiology

Submitted by JOHN E. MOSELEY, M.D.

New York, N. Y.

CASE NO. 224

A newborn Puerto Rican male was observed at two days of age to have a distended abdomen and to occasionally vomit small quantities of a greenish fluid. Although he had passed some meconium on the first and second days of life, the abdominal distention was increasing. No abdominal masses could be palpated. A roentgen examination of the abdomen showed dilatation of numerous loops of bowel (Fig. 1). In the erect position, there were multiple fluid levels. It could not be determined with certainty whether the gas was confined to the small bowel or was present in both small and large bowel. After insertion of a nasogastric tube and the administration of intravenous fluids, a Hypaque meal study was made by injection of the contrast substance through the nasogastric tube into the stomach. The Hypaque outlined a moderately dilated small bowel with no evidence of obstruction (Fig. 2). The contrast substance was within the colon at approximately three hours. The colon was not distended and the patient was noted to pass some of the contrast material through the rectum. A Hypaque enema examination made the following day showed the rectum and colon to be of normal caliber throughout (Fig. 3). Gaseous distention of the small bowel was still noted. Evacuation of the contrast substance was relatively good. There was no abnormal retention of the Hypaque. Abdominal distention was relieved by intestinal intubation and the patient continued to pass stools normally. After seven days, the patient was discharged but the mother was told to report any significant changes in the baby's bowel function or any recurrence of abdominal distention. About one month later the infant was brought back to the hospital because of diarrhea, distention and fever. *E. coli* was cultured from the stools but, in spite of antibiotics and fluids, the diarrhea continued and, after ten days, the infant was noted to have developed periorbital and facial edema and pitting edema of the legs. The serum albumin was 2.9 Gm%. The

Case 244, Fig. 1. Examination of the abdomen shows numerous loops of bowel to be distended by gas. While most of the loops represent small bowel the possibility that some of the gas is in the colon cannot be excluded. The absence of gas in the rectum, however, should be noted.

Case 224, Fig. 2. Injection of Hypaque through a nasogastric tube shows the small bowel to be moderately dilated. Later films showed contrast substance in the colon at approximately 3 hours. No obstruction was demonstrated.

From the Department of Radiology, The Mount Sinai Hospital, New York, N. Y.



Fig. 2.



Fig. 1.

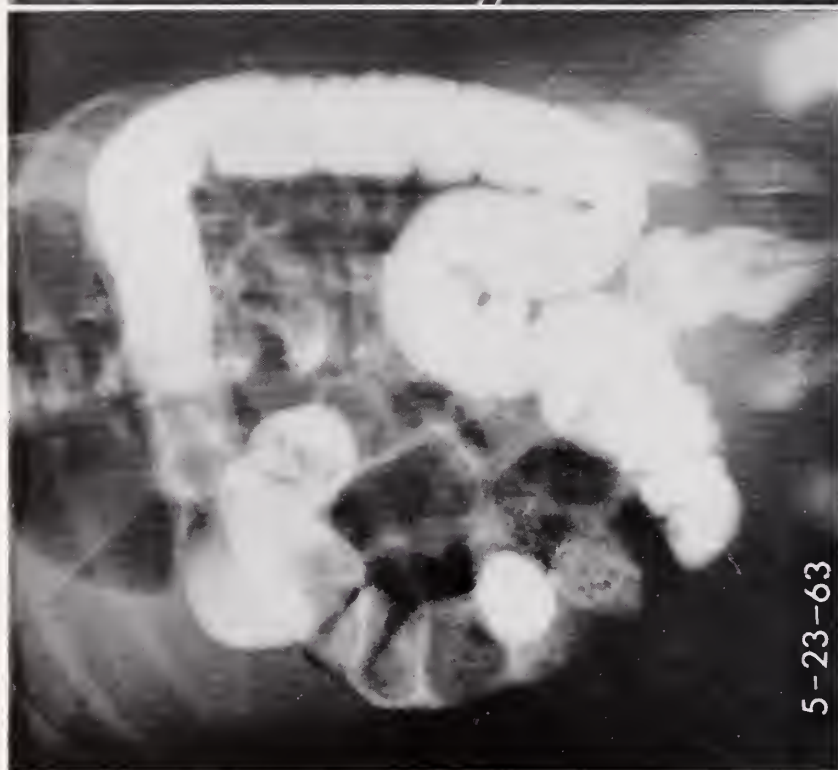


Fig. 3.

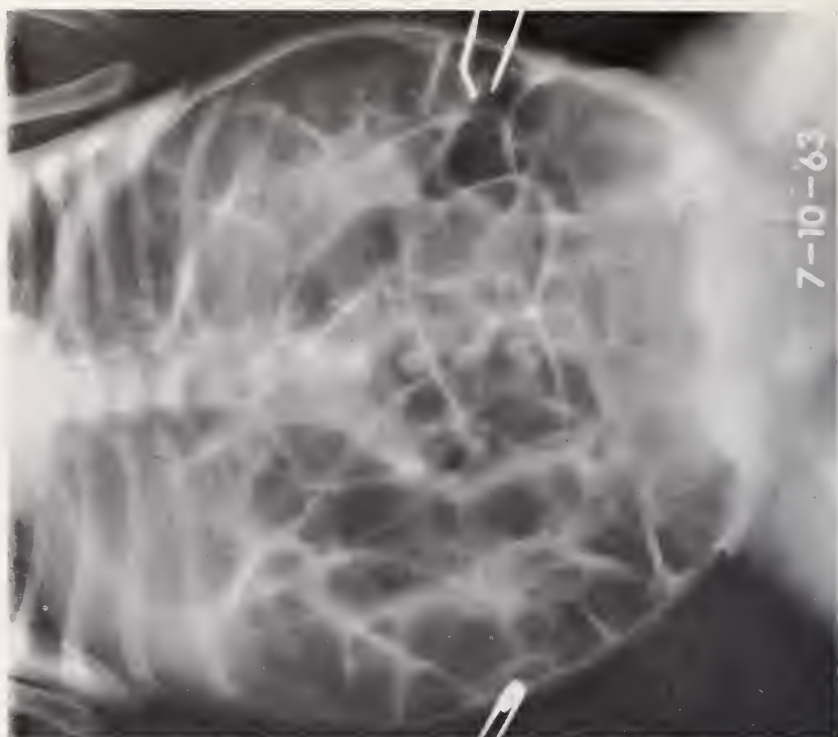


Fig. 4.



Case 224, Fig. 5. After injection of a small amount of Hypaque through the rectum a narrowed rectum and rectosigmoid is outlined (arrow) and the colon proximal to this is considerably dilated. These findings are consistent with aganglionosis involving the rectum and rectosigmoid.

Case 224, Fig. 3. Hypaque enema shows the rectum and colon to be of normal caliber throughout. Gaseous distention of small bowel loops may be noted. Evacuation of the contrast substance was good.

Case 224, Fig. 4. Examination of the abdomen shows rather marked distention of numerous loops of bowel. It is difficult to distinguish large and small bowel but the larger loops in the lower abdomen and along the left margin and upper abdomen probably represent dilated large bowel. No gas is demonstrated in the rectum.

globulin 2.6 Gm%. A tentative diagnosis of a protein-losing enteropathy was made. At this time, a roentgen examination of the abdomen showed considerable dilatation of numerous loops of what were interpreted to be both large and small bowel. No fecal material was demonstrated in the gas-filled loops and no gas was demonstrated in the rectum (Fig. 4). A small amount of Hypaque, given by rectum, outlined a narrowed rectum and rectosigmoid with dilatation of the colon proximal to the narrowed segment (Fig. 5). A diagnosis of Hirschsprung's disease was made. The baby was given intravenous fluids, albumin and antibiotics and a transverse colostomy was performed. There was marked improvement following the colostomy and the patient was discharged to return later for a Swenson pull-through procedure.

Case Report: INFANTILE HIRSCHSPRUNG'S DISEASE WITH ENTEROCOLITIS AND PROTEIN-LOSING ENTEROPATHY.

CASE NO. 225

With the assistance of S. DANIEL BLUM, M.D.

A 3 month old male infant was admitted to the hospital because of fever, diarrhea and abdominal distention. His past history indicated that he had been constipated since birth and, in fact, had passed no stool for several days after birth until attempts to dilate the rectum dislodged a large meconium plug. The mother reported that since that time the patient had been intermittently moderately constipated until about two weeks before this admission, when he developed fever and profuse diarrhea. In the hospital, stool cultures revealed a *Staph. aureus* coagulase positive. Toxic granulosis of the red cells was noted. The patient was treated with antibiotics and Kaopectate but the diarrhea did not subside. After evaluation of the previous history, it was considered likely that the patient was suffering from an enterocolitis secondary to Hirschsprung's disease. A barium enema done to confirm this impression disclosed narrowing of the rectum and rectosigmoid with dilatation of the colon proximal to the narrowed segment. (Figs. 1, 2.) This dilated portion, however, was localized and proximal to it the colonic lumen was again diminished in caliber. Some fine spiculation of the bowel margins was noted and the mucosa, where demonstrable, showed some edematous change. The appearance of the colon proximal to the dilated segment was consistent with an ulcerative colitis. A rectal biopsy showed an absence of ganglion cells. Following decompression by rectal tube, a right transverse colostomy was performed. A Swenson pull-through operation was delayed until the patient was ten months old. At that time, multiple biopsies established that the level of transition from normal ganglion cells to absence of ganglion cells was at the proximal rectosigmoid. Ten days after this operation, the patient developed another bout of enterocolitis which was successfully treated with intravenous fluids and antibiotics.

Case Report: ENTEROCOLITIS IN INFANTILE HIRSCHSPRUNG'S DISEASE WITH ROENTGEN APPEARANCE OF ULCERATIVE COLITIS.



Case 225, Fig. 1. Barium enema examination shows narrowing of the rectum and rectosigmoid (arrow). The distal sigmoid is dilated but the colon proximal to this dilated segment is diminished in caliber for a distance and then moderately dilated. There is a loss of haustral markings and some spiculation is noted along the bowel margins. The roentgen appearance proximal to the aganglionic segment is that of ulcerative colitis. Distended loops of small bowel are also demonstrated.

DISCUSSION

In older infants and in children the classic clinical manifestations of Hirschsprung's disease are chronic abdominal distention and more or less intractable constipation. In such patients, the roentgen findings on a properly performed



Case 225, Fig. 2. Postevacuation film shows incomplete emptying. In addition to marginal spiculation some nodularity of the mucosa can be seen.

barium enema examination are typically those of narrowing of the distal colon and rectum with dilatation of the colon proximal to the narrowed segment. Evacuation of the contrast substance is always poor. The clinical and roentgen features of Hirschsprung's disease in the newborn and very young infant, however, are quite different and it is important for early diagnosis to separate these two syndromes.

In the newborn infant, Hirschsprung's disease is usually manifested by abdom-

inal distention, vomiting and a period of obstipation. The clinical picture is that of intestinal obstruction. A flat film of the abdomen will usually show numerous loops of dilated intestine with multiple fluid levels in the erect position. At this age, it is frequently difficult or impossible to differentiate radiographically between distended large and small bowel, so that the roentgen appearance may well be considered consistent with a small bowel obstruction. For this reason, it is always advisable to outline the large bowel by contrast enema. In newborn infants with Hirschsprung's disease, however, the colon may outline normally, since changes in the caliber of the colon due to functional obstruction may not have developed at this early period. It is helpful in such circumstances to observe the degree of evacuation of the contrast substance since evacuation is usually poor and large amounts of the enema fluid are retained for 24 or 48 hours. Even without the typical distal narrowing and proximal dilatation of the colon on contrast enema, the clinical picture of intestinal obstruction with dilated loops of small bowel and a normal colon and rectum is sufficiently characteristic of Hirschsprung's disease to warrant a high index of suspicion and the performance of a rectal biopsy.

An understanding of the subsequent clinical course of the condition in these infants is also imperative for diagnosis and proper treatment. After relief of the obstructive manifestations, the infants usually experience a period during which the bowel movements are normal or there is mild constipation. After a few weeks, however, some of the patients develop a more classical syndrome of increasing constipation and abdominal distention and roentgen findings characteristic of aganglionosis. Many of them, however, contract a viral or bacterial enterocolitis and are then seen with abdominal distention, vomiting, fever and diarrhea. Such attacks may be acute and lethal if the primary disease is unsuspected, or they may be recurrent or chronic. If the neonatal history is unknown or not properly evaluated, nonoperative therapy may be inadequate and result in death of the patient. Without suspicion of aganglionosis, the diagnosis may be missed, even after autopsy. There is little doubt that some infants who have died from "diarrhea" have, in fact, succumbed to this frequent complication of Hirschsprung's disease.

Several interesting features are to be noted in the two cases described above. In the first case, although the infant developed abdominal distention and vomited small quantities of bile-stained fluid, there was no obstipation. Some meconium was passed on the first and second days prior to the enema. Radiographic examination of the colon in the newborn period failed to establish a roentgen diagnosis of Hirschsprung's disease (See Case 224, Fig. 3) and evacuation of the enema was considered to be within normal with no evidence of the stasis usually seen following enema examination in this disease. One month later, an enema with water soluble contrast substance demonstrated the diagnostic roentgen features of aganglionosis. The hypoproteinemia was interpreted as due to exudative enteropathy with protein loss into the intestinal tract. Feinberg *et al.* have recently reported four cases of exudative enteropathy in infantile Hirschsprung's disease (1).

In the second case, barium enema examination revealed the unusual findings of an aganglionic segment of rectum and rectosigmoid associated with ulcerative colitis. Pathologically, ganglion cells were absent up to the proximal rectosigmoid. Proximal to this area there is a segment of dilated colon. Above this the lumen is narrowed, there are fine marginal spiculations due to ulceration, and some cobblestoning of the mucosa can be appreciated. There is a loss of the haustral markings throughout, the appearance being that of an ulcerative colitis. In this case the colitis was considered to be specific and due to a *Staph. aureus* infection. In these severe forms of colitis changes may occur which are irreversible even after colostomy. Thus, colitis may persist if the patient survives.

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CASE NO. 226

This 3 year old female child weighed 4 lbs., 8 oz., when delivered at term. The pregnancy had been uneventful. Examination in the newborn period revealed no abnormalities except for a somewhat peculiar facies characterized by prominence of the eyes and slight puffiness of the eyelids. She gained weight well and was discharged from the hospital after twelve days. At the age of two months her pediatrician first noted that her liver and spleen were enlarged. At three months of age she had developed a noticeable pallor and hematologic work-up revealed a moderate anemia and many vacuolated lymphocytes and monocytes. A bone marrow smear showed scattered Niemann-Pick cells. At about one year of age papilledema and cherry red spots in the macular area of the ocular fundus were observed. The child, nevertheless, continued relatively well until one day prior to this admission at the age of three years, when dyspnea and cough were noted.

Physical examination on admission revealed marked pallor and lethargy. The respirations were somewhat labored. Auscultation of the lungs revealed scattered bilateral wet rhonchi and expiratory wheezes. The heart rate was 100 per minute. There was a grade 3 harsh systolic murmur along the left sternal border and at the apex. The spleen was enlarged, hard, and extended into the pelvis. The liver extended below the umbilicus. The reflexes were hypoactive. There was some atrophy of the lower extremities. Clubbing of the fingers was noted. The clinical impression was that of a pneumonitis, probably associated with congestive heart failure secondary to cardiac infiltration.

A roentgen examination of the chest showed an enlarged heart with pulmonary vascular engorgement but no definite infiltrations could be demonstrated. The hemoglobin was 11 Gm. There were 3,900 WBC with 68 polys, 12 bands and 17 lymphs. Traces of albumin were found in the urine. A roentgen skeletal survey showed a generalized demineralization of the bones. In the long bones, the medul-



Case 226, Fig. 1. Examination of the lower extremities shows marked demineralization. The cortices are thinned and the medullary cavities are widened. There is moderate failure of tubulation of the long bones.

lary cavities were widened and the cortices were thinned (Fig. 1). The ribs were widened with very thin cortical margins. The short tubular bones of the hands and feet were considerably demineralized with extremely thin cortices but they maintained relatively normal contours (Fig. 2). The skull was not abnormal.

The patient was digitalized and placed on penicillin therapy. By the sixth hospital day the fever was down to normal and remained that way. The child's distress was considerably diminished and her appetite began to improve. By the



Case 226, Fig. 2. The short tubular bones of the hand show widened medullary cavities, thinned cortices and marked demineralization.

eight day the patient had improved to an extent permitting discharge from the hospital.

Case Report: NIEMANN-PICK DISEASE.

DISCUSSION

Demonstrable bone changes occur in many cases of Niemann-Pick disease. Accumulation of large numbers of Niemann-Pick cells in the bone marrow result in widening of the medullary cavities, thinning of the cortices and diminished density of the bones. When the process is advanced there is moderate failure of tubulation of the long bones. Characteristically, roentgen changes are not noted in the diploic space of the skull. In many instances reticulogranular infiltrations may be seen in the lungs and, in some cases, extensive calcifications have been demonstrated in the adrenal glands.

This patient was diagnosed at the relatively early age of three months and has already survived for almost three years. Usually, the course is one of unremitting deterioration with death occurring within a few months. The prolonged survival of this patient may well account for the advanced nature of the bone changes noted.

ACKNOWLEDGMENT

This case is presented through the courtesy of Dr. Ralph Moloshok.

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CASE NO. 227

A six year old Negro girl was admitted to the hospital with a two month history of weakness, anorexia, lethargy and low grade fever. The past history was non-contributory. There was no history of contact with tuberculosis. Physical examination revealed normal height but the patient was 2 standard deviations below average in weight. Some conjunctival pallor was noted. The abdomen was distended. The liver was 1 fingerbreadth below the costal margin. A large mass could be palpated in the right upper abdomen. It extended across the midline and was separate from the liver. No other abnormalities were noted. Laboratory studies disclosed a hemoglobin of 8.2 Gm. WBC were 15,250 with slight shift to the left. There was a slight trace of albumin in the urine with occasional white blood cells. The erythrocyte sedimentation rate was 82 mm/hr. Tuberculin test of intermediate strength was markedly positive at 48 hours.

X-ray examination of the chest showed a widening of the superior mediastinal shadow to the right. The appearance was consistent with right paratracheal adenopathy (Fig. 1). Intravenous pyelography showed the right kidney to be displaced slightly laterally and slightly rotated. There was dilatation of the left collecting system and the left ureter was displaced upward and outward just below the uretero-pelvic junction (Fig. 2). These findings were interpreted as being due to a retroperitoneal mass or masses extending across the midline and displacing the right kidney and left ureter. A barium meal examination showed some dilatation of the descending duodenum. There was a small compression defect on the lower margin of the duodenum at the junction of the second and third portions and a much larger compression defect involving the distal duodenum up to the ligament of Treitz (Fig. 3).

Because of the positive tuberculin test, gastric washings and urine were sent to the laboratory for culture and the patient was scheduled for liver biopsy. It was felt, however, that this should be preceded by one week of INH and PAS antituberculous therapy. The patient became afebrile after 72 hours of therapy but the ESR and the WBC remained high. The liver biopsy was not diagnostic and the patient was scheduled for laparotomy. At surgery a mass of large nodes, matted together, were found at the site of the palpable mass. Frozen section examination showed these to be caseating tuberculous nodes. It was technically

impossible to remove them. The patient was continued on INH and PAS therapy, postoperatively. Three weeks after surgery the patient was discharged from the hospital to be followed on home therapy. Five weeks after surgery the patient was gaining weight and had a normal hemoglobin and an ESR of 31.

Case Report: TUBERCULOSIS OF ABDOMINAL AND MEDIASTINAL LYMPH NODES.



Case 227, Fig. 1. The superior mediastinum is widened to the left. Its left lateral margin is rounded and the appearance is consistent with left paratracheal adenopathy.

DISCUSSION

Tuberculosis of the abdominal lymph nodes may result from primary tuberculosis of the intestine or from seeding with tubercle bacilli through the bloodstream. Tuberculous abdominal nodes may compress adjacent loops of intestine with varying degrees of obstruction to the passage of their contents. Compression of the portal vein may result in ascites and dilatation of the superficial abdominal veins and pressure on the vena cava may cause edema of the lower extremities. Lincoln and Sewell have mentioned a case in which chylous ascites has resulted from compression of the thoracic duct.

Development of a palpable abdominal mass with evidence of intestinal compression and displacements of the kidney and ureter are not commonly seen to-



Case 227, Fig. 2. Intravenous urography shows the right kidney to be displaced laterally and rotated. The left collecting system is dilated and the left proximal ureter is compressed and displaced upward with partial obstruction (arrow). This was interpreted as being due to a large retroperitoneal mass or masses crossing the midline and displacing the right kidney and left ureter.

day as a result of tuberculous adenitis. For that reason the possibility of other retroperitoneal processes such as neuroblastoma and lymphoma were considered in this case. The patient's response to antituberculosis therapy, however, was



Case 227, Fig. 3. Barium meal examination shows dilatation of the descending duodenum. There is a compression defect on the lower border of duodenum at the junction of the second and third portions. The distal duodenum is markedly compressed with spreading and flattening of its mucosal folds. The presence of contrast substance in the hepatic flexure of the colon suggested the presence of a duodenocolic fistula but one could not be demonstrated at surgery.

strongly suggestive that both the mediastinal and abdominal lesions were acid fast in origin. The finding of tuberculous abdominal nodes at surgery, nevertheless, was not without surprise for some observers.

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The Angiographic Diagnosis of Occlusion of the Supraclinoid Portion of the Internal Carotid Artery

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Despite occasional difficulties in diagnosis (1 to 3), the angiographic appearance of a complete occlusion of the origin of the internal carotid artery in the neck is usually readily recognized by all arteriographers. Considerable more difficulty, however, is encountered in the interpretation of arteriograms showing cessation of flow of contrast medium at the intracranial portion of the internal carotid artery. The authors have recently presented seven patients with arteriographic findings indicating complete occlusion of the supraclinoid portion of the internal carotid artery elsewhere (4). An additional fifteen patients with supraclinoid carotid obstruction demonstrated by angiography have been reported in the literature (4). The purpose of this communication is to illustrate those features which allow an arteriographic diagnosis of supraclinoid carotid occlusion, and to discuss other conditions which may cause diagnostic difficulties.

Supraclinoid Carotid Occlusion: The clinical histories of the seven patients have been presented elsewhere (4). Their arteriograms, which are reproduced here through the permission of the editor and publishers of *Neurology*, appear as Figures 1 through 10.

Serial arteriography, with films obtained for at least six seconds after injection, is generally necessary for the arteriographic diagnosis of supraclinoid carotid occlusion. With a true occlusion an intracranial arterial "runoff" is present, and this allows contrast substance to leave the carotid after a few seconds. This "runoff" is usually the ophthalmic artery, but the posterior communicating and posterior cerebral arteries, and the anterior choroidal artery may also serve in this fashion. This arterial "runoff" is clearly visible in each of Figures 1 through 10. It is felt, therefore, that both the demonstration of an intracranial arterial "runoff" and the passage of contrast substance from the carotid after a few seconds is necessary for the arteriographic diagnosis of complete occlusion of the supraclinoid portion of the internal carotid artery. The demonstration of collateral circulation from the posterior cerebral to the anterior and middle cerebral arteries, as in Figures 4, 5 and 10, is a further confirmatory finding.

Faulty Injection of Contrast Media: A partial extraluminal injection of contrast substance may readily mimic the appearance of a supraclinoid carotid occlusion (1). Examples of this are shown in Figures 11 to 13. It is not clear why

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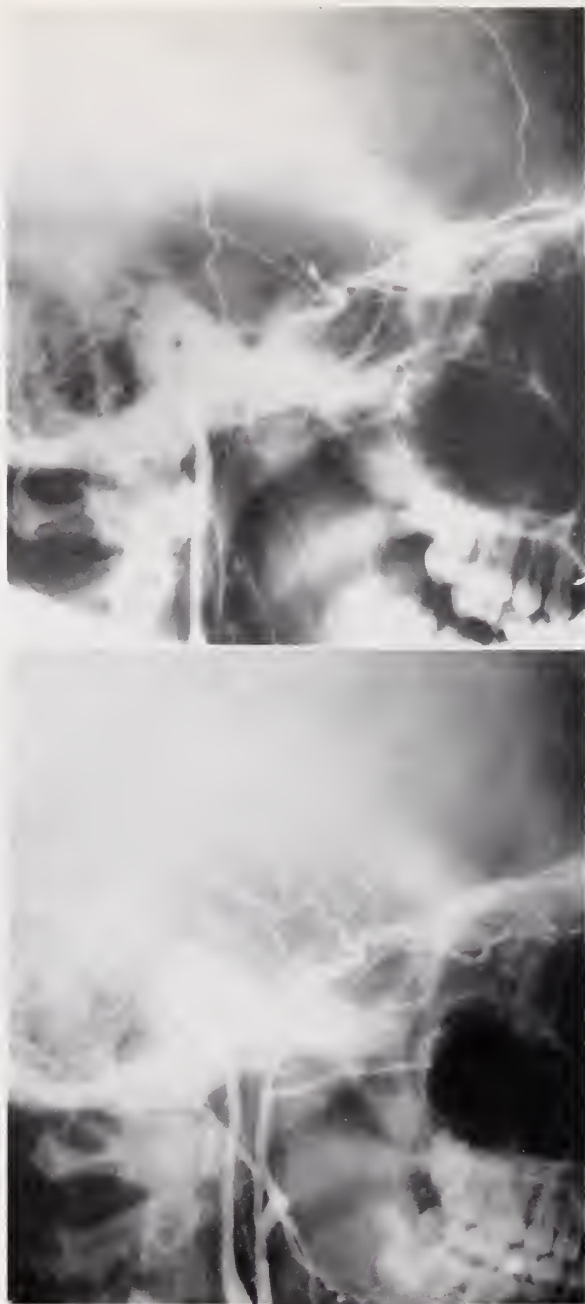


FIG. 1. (Top) Supraclinoid carotid occlusion. The ophthalmic and anterior choroidal arteries are visualized. Contrast substance was not seen in the carotid three seconds after injection.

FIG. 2. (Bottom) Same patient as in Fig. 1. Repeat arteriogram one month later. The posterior communicating and posterior cerebral arteries are now visualized.



FIG. 3. Supraclinoid carotid occlusion. The ophthalmic and anterior choroidal arteries are visualized. Contrast substance was not seen in the carotid four seconds after injection.



FIG. 4. Supraclinoid carotid occlusion. The ophthalmic, posterior communicating and posterior cerebral arteries are visualized. A faint trickle of contrast medium has entered the first portion of the anterior cerebral artery.

the resultant arteriographic findings following faulty injection frequently resemble supraclinoid carotid obstruction. Possible explanations include "spasm" of the artery from the trauma of the injection or dissection of the contrast medium within the carotid arterial wall up to the point of bifurcation of the artery at its supraclinoid location. Another possibility is reduction of the intra-arterial pressure by the faulty injection so that significant intraluminal contrast substance can not advance further than the supraclinoid portion, where



Fig. 5. Same injection as in Fig. 4, but exposure obtained three seconds later. Contrast substance is no longer seen in the carotid artery. Collateral circulation from the posterior cerebral to the middle and anterior cerebral arteries is shown.

it is so diluted by blood coming from the anterior or posterior communicating arteries as to lose its opacity. (A severe stenosis of the cervical carotid artery may also reduce the pressure in the intracranial portion of the artery thus preventing the flow of significant amounts of contrast medium from the supraclinoid region. An example of this is shown in Figure 14.)

This spurious appearance of a supraclinoid carotid occlusion may be detected by the persistence of contrast substance in the carotid artery during all exposures in a serial study, and usually by the lack of visualization of the ophthalmic, anterior choroidal or posterior communicating arteries. Neither of these findings are absolute. Persistence of contrast media in the carotid throughout

all phases of the study may be seen in patients who are hypotensive or who have acutely increased intracranial pressure (see below). Figure 13 is an example of a faulty injection which resulted in opacification of the posterior communicating and posterior cerebral arteries. For adequate diagnosis the films must include visualization of the needle in the neck. Only by this means



FIG. 6. Supraclinoid carotid occlusion. The ophthalmic and anterior choroidal arteries are visualized. Contrast substance was not seen in the carotid three seconds after injection.

will the faulty injection be detected and complete interpretation of the arteriogram allowed.

Other Causes for Diagnostic Difficulties: The occurrence of arterial "spasm" following an acute rupture of an intracranial aneurysm has been adequately documented (5). Such "spasm" may occur at the supraclinoid portion of the internal carotid artery, as in Figure 15, and if severe enough, may not allow visualization of the aneurysm or of the anterior and middle cerebral arteries. These findings may readily be confused with a true supraclinoid carotid occlusion, and only the clinical history, lumbar puncture and repeat arteriography

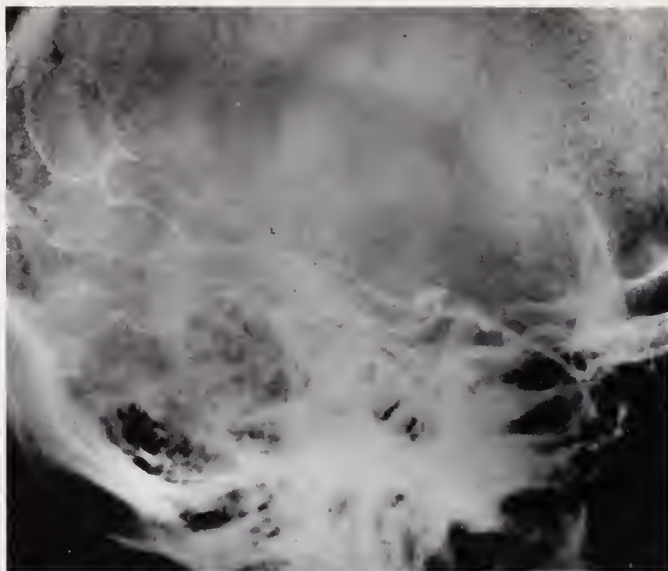


FIG. 7. Supraclinoid carotid occlusion. The ophthalmic, posterior communicating and posterior cerebral arteries are visualized.



FIG. 8. Supraclinoid carotid occlusion. The ophthalmic, posterior communicating and anterior choroidal arteries are visualized. Contrast substance was not seen in the carotid three seconds after injection.



FIG. 9. (Top) Supraclinoid carotid occlusion. The posterior communicating, distal portion of the basilar and both posterior cerebral arteries are visualized. Contrast substance was not seen in the carotid three seconds after injection.

FIG. 10. (Bottom) Same injection as in Fig. 9, but exposure obtained two seconds later. Retrograde visualization of branches of both the anterior and middle cerebral arteries can be seen. The opacification in the anterior cranial fossa represents an extracranial vessel.

will allow the proper diagnosis. Some authors (6) have suggested that abrupt blockage of flow at the supraclinoid portion of the internal carotid artery is evidence for "spasm" even without intracranial hemorrhage.

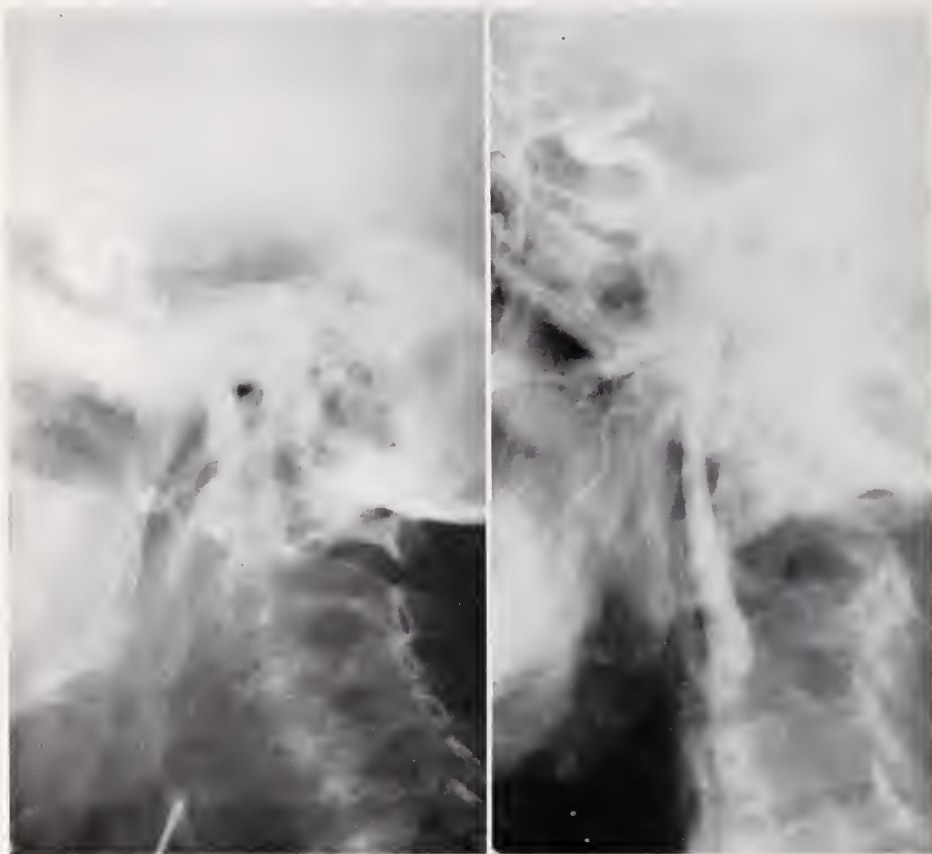


FIG. 11. (Left) Common carotid arteriogram shows an extraluminal injection which mimics supraclinoid obstruction of the carotid. There is no opacification of the ophthalmic, anterior choroidal and posterior communicating arteries, and the contrast substance persisted in the internal carotid artery for at least seven seconds.

FIG. 12. (Right) Common carotid arteriogram shows an extraluminal injection which might be confused with an occlusion of the supraclinoid portion of the internal carotid. In addition to the features described for Fig. 11, the faulty injection in the neck is shown. The anterior and middle cerebral arteries were opacified when the study was repeated following re-insertion of the needle.

Nonvisualization of the middle and anterior cerebral arteries during angiography of patients with acute intracranial hypertension may also be misdiagnosed as an occlusion of the supraclinoid portion of the carotid. Repeat angiography following reduction of intracranial pressure may be necessary for diagnosis (7).

A middle cerebral artery occlusion in a patient with an anomalous circle

of Willis, in which both anterior cerebral arteries are derived from the contralateral carotid artery, will also mimic a supraclinoid carotid occlusion. The demonstration of collateral circulation from the posterior to anterior cerebral arteries may be necessary for an absolute diagnosis of complete occlusion of the supraclinoid portion of the internal carotid artery.



FIG. 13. Common carotid arteriogram shows a partial extraluminal injection with apparent cessation of flow of contrast substance at the supraclinoid portion of the internal carotid artery. The posterior communicating and posterior cerebral arteries are visualized. Contrast media remained in the carotid for at least seven seconds. The anterior and middle cerebral arteries were shown by another injection.

SUMMARY

A differential diagnosis of the angiographic features of occlusion of the supraclinoid portion of the internal carotid artery has been presented. A definite diagnosis of supraclinoid carotid obstruction requires the passage of contrast medium from the carotid in a few seconds, and an intracranial arterial "runoff" (the ophthalmic, posterior communicating—posterior cerebral or anterior choroidal arteries). The injection of contrast substance in the neck must be



FIG. 14. Common carotid arteriogram shows severe stenosis of the origin of the internal carotid artery and no flow of contrast beyond its supraclinoid portion. (The patency of the supraclinoid portion was not proven in this case.)



FIG. 15. Common carotid arteriogram shows localized "spasm" at the supraclinoid portion of the carotid artery and an aneurysm arising from the first portion of the anterior cerebral artery.

clearly intraluminal. The demonstration of collateral circulation is also of diagnostic value.

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The Antepartum Diagnosis of Osteogenesis Imperfecta Congenita: A Report of Two Cases Recognized in Utero

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Full-blown osteogenesis imperfecta in the newborn infant is uncommon. Potter (1) reported one case in 60,000 births, Posner and Goldman (2) one in 40,000 and Freda *et al.* (3) one in 21,000. In this congenital form of the disease, in contradistinction to osteogenesis imperfecta tarda, advanced skeletal abnormalities are present at birth. Consequently, the condition may be recognized readily on roentgenograms of the maternal abdomen and pelvis made during the third trimester of pregnancy. The desirability of an antepartum diagnosis is of more than academic interest. The fetus, in this disease, has almost always suffered multiple fractures prior to the onset of labor. Armed with the awareness that an unusually fragile fetus is present, the obstetrician may modify the method of delivery to minimize additional trauma. Extreme gentleness is also required in resuscitation. Since a superficial examination of the infant may not suggest osteogenesis imperfecta to the pediatrician, a prenatal diagnosis may be a major factor in maintaining viability. The majority of these infants die within a few days despite expert and gentle care. To those babies who survive the immediate newborn period, some hope is afforded by new techniques of realignment and intramedullary fixation of fractures (4).

A review of the obstetrical literature in the past decade has uncovered a number of thorough discussions of the in utero diagnosis of osteogenesis imperfecta (2, 5, 6, 7). Only two such articles were found in the radiologic literature, both by British authors (8, 9). It was felt that a re-emphasis of this rare but important entity might be of value.

PATHOLOGY

It has long been maintained that osteogenesis imperfecta is the result of a deficiency both in enchondral and periosteal bone production. As pointed out by Rubin in his reclassification of bone dysplasias, deficiencies in two distinct areas rarely, if ever, occur in a single disease (10). According to Rubin, osteogenesis imperfecta is a pure diaphyseal dysplasia and the pathologic changes are solely the result of deficient periosteal bone formation. Thus, the cortex of the bone is extraordinarily thin. These thin cortices fracture with minimal trauma. The marked deformities of osteogenesis imperfecta are the result of an incessant cycle of fracture and healing occurring in utero and throughout the period of infancy. Callus formation is normal and non-union

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rarely occurs. Since the fundamental deficiency is in the periosteum, the epiphyses and cartilagenous areas are intrinsically normal.

The serum calcium and phosphorus levels are unaltered. Alkaline phosphatase values are elevated transiently during fracture healing, but invariably return to normal.

GENETICS

The genetic transmission of osteogenesis imperfecta is not fully understood at present. There is general agreement that the tarda form is transmitted by an autosomal dominant gene. Transmission in osteogenesis imperfecta congenita is less amenable to study, since patients with this form of the disease have not been known to reproduce. Some authorities state that the disease is transmitted by a recessive gene while others report it is the result of spontaneous mutation. In only about one-quarter of cases of the congenita type is there a family history of the stigmata of either form of the disease (3, 11). Since these stigmata may be so mild as to be overlooked and since three-quarters of cases have a negative family history, it is rarely possible to anticipate the disease prior to birth.

ROENTGEN FINDINGS

An antenatal diagnosis may be established from pelvimetry studies, placentography or any roentgenograms in which part or all of the fetus is visualized. All reported cases have been examined late in pregnancy, usually at thirty-four weeks or beyond. There is no information on the earliest date at which a diagnosis is feasible. Legitimate indications for a pelvimetry are frequently present. These include a positive family history, polyhydramnios, breech presentation and fetal distress. In some instances, the soft, compressible fetal skull is mistaken for the breech. The fetus may appear unusually small by palpation. In one of our cases, the patient experienced severe hemorrhage as the result of premature placental separation and secondary hypofibrinogenemia. There is no reason to believe that this complication was related to the abnormal fetus.

The roentgen findings are characteristic. The fetus appears smaller than normal and frequently has assumed the so called "Buddha" attitude (6). The bony structures are markedly demineralized. The calvarium may be barely discernible; in contrast, the petrous bones are relatively well mineralized and are readily identified. The tubular bones are demineralized, shortened and show numerous angulations. In severe cases, the long bones are pleated in accordion-like fashion. The shafts of the tubular bones are usually widened and show loss of normal diaphyseal constriction. The ribs show changes identical to those seen in the long bones. Occasionally, the fetal skeleton seems studded with small densities. These represent areas of exuberant callus formation. When visible, the epiphyseal centers appear normal.

In osteogenesis imperfecta tarda, the fetal skeleton is normal in appearance and a prenatal diagnosis is not feasible.

DIFFERENTIAL DIAGNOSIS

The antenatal diagnosis of osteogenesis imperfecta congenita is not difficult. The commonest cause of a poorly visualized skeleton is fetal movement. Consequently, a repeat abdominal roentgenogram should be made in doubtful



CASE 1, FIG. 1. Anteroposterior view of abdomen. Fetal spine (black arrow) barely discernible. Fetal head (white arrows) seen as soft tissue shadow only. Small parts not visible.

cases. Hypophosphatasia has not, to our knowledge, been diagnosed in utero. In this condition, marked demineralization of the skull and skeleton is present. However, widening of tubular bones and multiple skeletal fractures are not present. The epiphyseal areas are most severely affected, exhibiting advanced rachitic changes. Chondrodystrophy and achondroplasia, while superficially similar, are distinguished by their normal bone density. In cleidocranial dysostosis, the skull is very translucent; however, the spine and long bones are normal. The anencephalic fetus has normal mineralization and a small, dense, triangular skull. Hydrocephalus, ectromelia, phocomelia and fetal death bear no resemblance to osteogenesis imperfecta.

CASE REPORTS

Case 1. This 32 year old female, gravida IV para II, Ab 1, was admitted to the hospital in her thirty-sixth week of pregnancy, leaking fluid and having irregular contractions. Her prenatal course had been complicated by mild anemia, excessive weight gain and pretibial edema.



CASE 1, FIG. 2. Roentgenogram of fetus. Calvarium virtually uncalcified. Tubular bones short, wide and angulated. Cortices extremely thin.

There was no history of skeletal disease in the patient's family or in that of her husband. Two children were normal.

Physical examination revealed a blood pressure of 130/90 and minimal leg edema. The uterus was of term size and was tense and irritable. Fetal heart tones were heard in the right lower abdomen at a regular rate of 140 per minute. On vaginal examination the cervix was not effaced. No presenting part could be palpated. An anteroposterior roentgenogram of the abdomen was obtained to evaluate fetal position.

Roentgen findings: The uterus was enlarged to the level of the first lumbar vertebra. The fetal skeleton was markedly demineralized. The fetal spine was

faintly visible just to the right of the maternal vertebral column. The calvarium was represented by a soft tissue density overlying the maternal sacrum. The diagnosis of osteogenesis imperfecta was suggested. Because the extremities were not visible, it was felt that hypophosphatasia could not be excluded.

Immediately upon her return from the Radiology Department, the patient passed approximately 200 cc of blood per vaginam. Six hours later hematemesis and hematuria occurred. The serum fibrinogen level was 165 mg per 100 cc. It



CASE 2, FIG. 3. Pelvimetry, lateral view. Breech presentation. Fetal skeleton extremely demineralized. Petrous bones (arrow) relatively well mineralized.

was felt that the patient was suffering from hypofibrinogenemia secondary to abruptio placenta. Because of these findings and the knowledge of an abnormal fetus, the patient was prepared for cesarean section with the administration of 500 cc of fresh whole blood and 4 Gm of fibrinogen. A live female infant, weighing 4 lb. 6 oz., was delivered by low cervical transverse cesarean section. The infant had the typical clinical and roentgen features of osteogenesis imperfecta. In addition, a harsh, grade IV apical systolic murmur was present. Six hours later the infant died. Post mortem examination confirmed the presence of osteogenesis imperfecta. A membranous ventricular septal defect was also present.

Case 2. This 22 year old female, gravida IV para III was admitted to the hospital in early labor.

The family history was negative for skeletal disease. Three children were normal.

On physical examination, the breech was palpable as the presenting part. Because of the breech presentation, x-ray pelvimetry was obtained.



CASE 2, FIG. 4. Roentgenogram of fetus. Note similarity to Case 1, Fig. 2. Multiple healing fractures are present.

Roentgen findings: Despite marked skeletal demineralization, the breech was faintly visible in the maternal pelvis. The fetal extremities were shortened and angulated and the tubular bones appeared unusually wide. While the external contour of the skull was barely visible, the petrous bones were relatively dense and were easily seen in the upper abdomen.

A 6 lb, 10 oz, female infant was born by spontaneous breech delivery. Clinical and roentgen findings were typical of osteogenesis imperfecta. At the time of preparation of this manuscript, the infant, though deformed and feeble, was still alive.

SUMMARY

Two cases are reported of osteogenesis imperfecta congenita diagnosed in utero. In each case, the diagnosis was based primarily on extreme demineralization of the fetal skeleton. Associated findings are shortening, widening and angulation of the long bones, relative radiodensity of the petrous bones and a normal appearance of the epiphyses. Modern pediatric and orthopedic management of this disease has increased the neonatal salvage and improved the ultimate prognosis. A prenatal diagnosis may be of great importance in the delivery of a viable infant and the institution of safe resuscitation. The great majority of cases presumably are the result of spontaneous mutation and cannot be anticipated on genetic grounds.

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Neonatal Gastric Perforation

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Perforation or rupture of the stomach during the first month of life has been observed with increasing frequency since the original description of this entity in 1826 by A. E. von Siebold (1). He described a premature infant who died on the second day of life; at autopsy, a perforation within an area of gangrene on the lesser curvature of the stomach was found.

A review of the literature has disclosed 159 cases of gastric perforation in the neonatal period. 103 were operated upon and 38 survived. In the nonoperated group of 56 patients there was only one survivor (Table I). In 1929 Stern *et al.* attempted surgical repair of a gastric perforation in a newborn (2). The infant died because of reperforation which occurred in the immediate postoperative period. In 1950 Léger and his associates reported the first successful surgical treatment of a ruptured stomach in a full-term newborn (3). Two years later Beattie and Bohan reported the first premature baby who survived the operation (4).

This communication deals with an analysis of the literature on gastric perforation during neonatal life, including three case reports:

1. A case of gastric perforation which was diagnosed and treated promptly.
2. A case of pneumoperitoneum; the site of perforation was not found at operation.
3. A case of seromuscular tear of the stomach wall with herniation of the mucosa and impending rupture.

All three infants survived.

INCIDENCE

Among 1000 necropsies of newborns in the Maternity Clinic of Havana (1944–1955) there were two neonates with perforation of the stomach (5). 1778 autopsies in infants of two months or less were performed at the Institute of Pathology of the University of Tennessee (1953–1958) and neonatal gastric perforation was found in 4 instances, an incidence of 1:444 or 0.25 per cent (6).

In the last decade (January 1953–December 1962) 46,977 babies were delivered at The Mount Sinai Hospital. Autopsies were performed on 685 stillborn and 726 infants who died in the neonatal period. There was no case of gastric perforation in the autopsy records.

PRENATAL FACTORS

Minor and major complications of pregnancy were recorded in less than one-third of the cases. Toxemia (mild to severe), abruptio placentae, syphilis (treated or active), chronic nephritis, rheumatic heart disease, emergency

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cesarean section, breech extraction, face presentation, difficult low forceps, and polyhydramnios were recorded. In 13 instances the infant was one of twins.

Table II shows the racial distribution; this includes 14 presumably white babies born in European countries; 5 infants were born in hospitals with predominantly Negro populations; both groups were classified under "not recorded."

The sex distribution is shown in Table III.

TABLE I
Reported Cases (1826-1963)

Total Number of Cases	159
Nonoperated Cases	56
Cases Treated Surgically	103
Number of Survivors	39
Overall Mortality	75.47%

TABLE II
Racial Factors

Negro	62
White	32
Yellow	1
Mestizo	1
Puerto Rican	1
Not Recorded	62
	159

TABLE III
Sex

Male	64
Female	78
Not Recorded	17
	159

MATURITY

Table IV shows the distribution of premature and full-term infants. Three babies were classified as premature on the basis of their body weight at autopsy.

To simplify the classification, infants with a birth weight of 2500 grams or more were considered full-term and infants under 2500 grams were considered premature.

PATHOGENESIS

The various pathogenetic factors are summarized in Table V.

Peptic ulcer: Until 1943 acute or chronic peptic ulcer was thought to be the

basic disease which ultimately led to perforation (2-20, 31, 48). However, histological proof of peptic ulcer was recorded only in a few cases. In the remainder of the cases there was only presumptive evidence of acute or chronic ulceration.

"*Congenital muscular deficiency*" of the gastric wall was recorded in 35 cases (6, 21-41, 72, 82). In 22 cases, there was histological evidence of partial or complete absence of muscle fibers on sections of the wall of the stomach adjacent to or at a distance from the site of perforation. In the remaining 13 cases,

TABLE IV

Maturity

Premature	66
Full-term	53
Weight Not Recorded	40
	159

TABLE V

Presumed Pathogenetic Factors

	No. of Cases
Peptic Ulcer (Acute or Chronic)	33
"Congenital Muscle Defect"	35
Rupture of Diverticulum	4
Distal Obstruction	15
Tube Trauma	12
Pneumatic Pressure	6
Septicemia	5
Phlegmon of Stomach	1
Neurogenic	2
Anoxia	2
Birth Trauma	1
Volvulus of Herniated Stomach	1
Cause Unknown	53
	170*

* More than one factor was considered to be the cause in some of the cases.

thinning of the stomach around the site of perforation or in multiple areas of the wall of the stomach was considered presumptive evidence of "muscle defect." This gross finding was recorded either at the time of operation or at autopsy. Full-thickness biopsies of the gastric wall at the site of perforation were taken in very few instances.

Gastric diverticula: Four ruptured diverticula were found, all of them localized on the greater curvature aspect of the fundus close to the cardia. Because of histological absence of the muscular layer in the diverticular wall, 3 of these cases (31, 42, 43) were thought to be the result of a "congenitally defective" muscular coat in the region of the diverticulum. In the fourth case (44) of

ruptured diverticulum, all gastric layers around the site of perforation were intact.

Distal obstruction due to atresia of the pylorus or duodenum was recorded in 4 cases (5, 22, 42, 69); congenital stenosis at various levels of the gastrointestinal tract was found in 11 instances (5, 9, 11, 13, 15, 45-48, 74). In both types of obstruction proximal dilatation, including the stomach, was considered a factor contributing to the gastric perforation.

Tube trauma: Perforation of the stomach due to trauma by nasogastric tube was proved in 2 instances (31, 50) and was presumed to be the cause in 10 cases (6, 25, 31, 35, 47, 49, 50, 66). Nasogastric intubation with a soft rubber tube or polyethylene tube was carried out for aspiration or gavage feedings in 42 cases; in the majority of operated cases, a nasogastric tube was used as a preoperative or postoperative measure. A case of perforation of the stomach caused by tube trauma was described by McLaughlin (50). "An infant underwent repair of a tracheo-esophageal fistula on the 4th day of life; a polyethylene catheter was passed through the site of anastomosis and carefully positioned in the cardia of the stomach. On the 4th postoperative day, the polyethylene catheter was seen emerging through the umbilicus. Iodized oil was given and was seen, radiographically, outside of the gastric pouch." Because of the satisfactory clinical condition of the child, operative intervention was not carried out and the infant survived.

Potter described a case in which accidental introduction of a tracheal catheter into the esophagus and stomach may have been the cause of perforation (25).

Pneumatic pressure produced by mechanical resuscitation (E & J machine) and tight-fitting oxygen mask, leading to overdistention and perforation of the stomach was recorded in 4 cases (16, 51). The same mechanism as a possible cause of perforation of the stomach was mentioned in 2 instances (51, 52).

Septicemia, as evidenced by positive blood cultures, was presumed to account for the perforation in 5 cases (31, 53, 54, 78); in one instance a phlegmon of the stomach was attributed to overwhelming staphylococcal infection (55).

Neurogenic factor: The association of gastric perforation with intracranial hemorrhage was emphasized in 2 instances (56, 57).

Anoxia (16, 58), *birth trauma* (59) and *volvulus of the herniated stomach* (60) were presumed to be the cause of perforation in isolated cases. Stress ulcer was infrequently referred to as a possible etiologic factor. Systemic mucormycosis (40) was the cause of perforation in one case not included in this series; it is thought that invasion of the stomach wall by *Mucoraceae* may lead to local infarction, ulceration and perforation.

The cause was unknown in 53 cases of gastric perforation (16, 24, 25, 31, 35, 48, 58, 61-83). Some of these cases were previously classified "idiopathic" perforation of the stomach.

CLINICAL FEATURES

A variety of symptoms and signs have been recorded. However, certain signs appear with great constancy. With few exceptions these children appear normal

at birth. Premature infants constitute more than half of the recorded cases. Passage of meconium and transitional stools occurs normally. Absence of meconium stools was found in only one case. The onset of symptoms occurs within the first few days of life (Fig. 1). Rarely the onset of the illness was manifested after the first week of life. One infant became ill on the thirtieth day of life. Refusal of feedings is an early sign and is usually followed by vomiting and distention of the abdomen.

In a significant number of cases labored respirations and/or cyanosis preceded the onset of abdominal signs and suggested the incorrect diagnosis of acute pulmonary or congenital heart disease. Abdominal distention is the most constant and predominant clinical feature. The abdomen remains soft and tympanitic. There was only one instance in which abdominal rigidity was recorded.

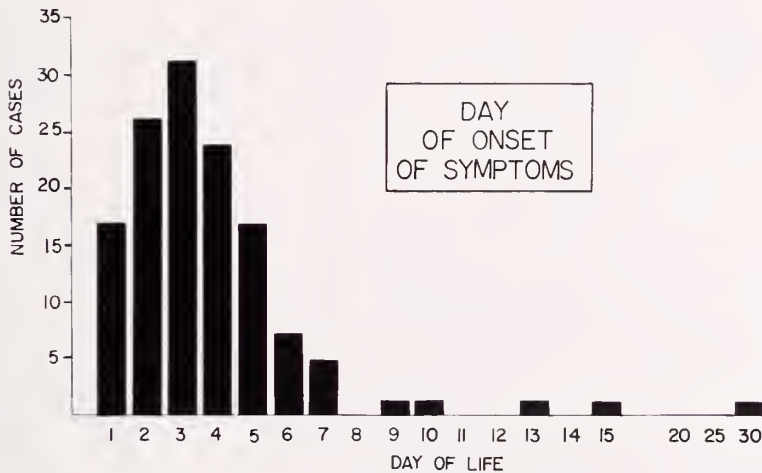


Fig. 1. Onset of symptoms confined mainly to first week of life.

Diminution or complete absence of peristaltic sounds was recorded in a small number of cases.

Absence of liver dullness was registered in 4 cases.

Blood in the vomitus or stool was a relatively frequent finding. In 12 babies, blood was noted in the vomitus and, in 4 infants, the vomitus was described as coffee ground. In 9 cases, there was gross evidence of blood in the stool and there were 7 instances of melena.

Erythema and edema of the lower abdominal wall was seen in 8 cases. In 4 instances, involvement of the external genitalia was observed. Emphysema of the lower abdominal wall was noted in 2 infants. In 5 babies the veins of the abdominal wall were prominent. Rare findings include diarrhea (3 cases), jaundice (7 cases), hepatomegaly (2 cases) and periumbilical erythema (2 cases).

The temperature and blood studies were of no diagnostic value.

ROENTGENOLOGICAL ASPECT

The first radiographic diagnosis of spontaneous pneumoperitoneum in a newborn infant was made by Assmann in 1922 (84). He described a massive collection of air around the liver, spleen and the intestine. At autopsy a perforation of the duodenum was found.

The demonstration of free air, free fluid or the combination of both is simple

TABLE VI
X-ray Findings (Operated Cases)

Pneumoperitoneum	71
Hydropneumoperitoneum	20
Hydroperitoneum	2
Misinterpretation of Scout Film in Supine Position	<div style="display: flex; align-items: center;"> <div style="margin-right: 10px;">{</div> <div style="margin-right: 10px;">4</div> <div style="display: flex; flex-direction: column; align-items: flex-start;"> <div>→A. Distention of large and small bowel</div> <div>→B. No pathological findings</div> <div>→C. No pathological findings</div> <div>→D. Picture of small bowel obstruction</div> </div> </div>
X-rays Negative for Perforation	4
X-rays Not Taken	2
	103

TABLE VII
X-ray Findings (Nonoperated Cases)

No X-rays Taken	30
Pneumoperitoneum	16
Misinterpretation of Scout Film in Supine Position	<div style="display: flex; align-items: center;"> <div style="margin-right: 10px;">{</div> <div style="margin-right: 10px;">4</div> <div style="display: flex; flex-direction: column; align-items: flex-start;"> <div>→A. No free air seen</div> <div>→B. No free air seen</div> <div>→C. Distention of stomach, small and large bowel</div> <div>→D. Distention of large and small bowel</div> </div> </div>
X-rays Negative for Perforation	2
No X-ray Findings Recorded	4
	56

when films are taken in the upright position. Tables VI and VII show the frequency with which this diagnostic tool was used.

In the nonoperated group x-rays were not taken in 53.57 per cent of the cases. Seven infants died before the diagnostic significance of pneumoperitoneum became appreciated.

The presence of free air or free fluid in the peritoneal cavity can be easily missed, if the films are taken in the supine position only (Tables VI and VII). An upright film constitutes the most essential part of the roentgen examination. Coutel and his associates emphasized the diagnostic significance of the absence of the gastric bubble on scout films of the abdomen (29). This finding was re-

ported in 5 additional instances of gastric perforation. The same authors state that the gastric air bubble remains visible in cases of meconium peritonitis, hematogenous peritonitis and intestinal perforation other than gastric.

Rare radiographic findings include subcutaneous emphysema in the region of the abdomen and in the area of the scrotum (in 2 instances). In one case (51), a left diaphragmatic hernia containing a ruptured stomach was misinterpreted as tension pneumothorax involving the left chest.

USE OF CONTRAST MEDIA

In 14 cases a contrast material was used as a diagnostic aid in an attempt to exactly localize the site of perforation. Tables VIII and IX show the nature of the contrast media used and the contribution of these agents to precise roentgen

TABLE VIII
X-ray Findings (Use of Contrast Media)

Substance Used	No. of Cases	No. of Survivors
Barium.....	8	0
Iodized Oil.....	6	4

TABLE IX
Diagnostic Aid from Use of Contrast Media

	No. of Cases
Exact Localization of Site of Perforation.....	6
Approximate Localization of Site of Perforation.....	3
Use of Dye Noncontributory.....	5

diagnosis. The dye was given either in form of a meal or injected through a nasogastric tube.

None of the infants in whom barium was used survived. The use of Lipiodol in the case of Léger (3), the very first to survive the operation, permitted the exact localization of the site of perforation and contributed to the survival of the child.

SURGICAL CONSIDERATIONS

Once the diagnosis of gastric perforation is suspected or established, exploratory celiotomy should be carried out without any delay. Nasogastric suction (gentle introduction of the tube!) to decompress the stomach and diminish leakage of gastric contents into the free peritoneal cavity should be instituted. Correction of the fluid and electrolyte imbalance is an important preoperative measure and must be done without loss of valuable time. Occasionally, paracentesis might help to decrease the intra-abdominal pressure and relieve, to a certain extent, the respiratory distress.

Time interval: Table X shows the relationship between the rate of survival and the time interval between onset of symptoms and operation.

Extremely valuable time was lost in 10 cases because the clinical diagnosis of intestinal obstruction was entertained and radiographical investigation and ultimate necessary treatment delayed. In 2 cases (78) an incarcerated inguinal hernia was diagnosed. Urinary retention (46), cerebrospinal hemorrhage (29) and intra-abdominal cyst (74) were suspected in each respective case.

After employment of the roentgen diagnostic facilities, the preoperative diagnosis of perforated viscus was made in 85 cases, perforated stomach in 7 cases and

TABLE X
Recorded Time Interval Between Onset of Symptoms and Operation

	No. of Cases	Average	Maximum	Minimum
Survivors	21*	13 $\frac{3}{4}$ hours	2 days	2 hours
Nonsurvivors	37*	45 $\frac{1}{3}$ hours	13 days	2 hours

* In the remainder of cases the time interval was not recorded.

TABLE XI
Preoperative Diagnoses

	No. of Cases
Perforated Viscus	85
Perforated Stomach	7
Intestinal Obstruction	4
Pyloric Obstruction	1
Peritonitis	1
Acute Abdomen	1
Mass in Left Flank	1
No Diagnosis Recorded	3
	103

intestinal obstruction in only 5 cases; acute abdomen and peritonitis was suspected in 2 instances. On one occasion a mass in the left flank was diagnosed. A preoperative diagnosis was not recorded in 3 cases (Table XI).

Anesthesia: (See Table XII.) Local infiltration anesthesia was used in 20 cases; in one instance intercostal block was employed. A general anesthetic agent was used in 30 cases. Vargas *et al.* (31) who reported 8 surgically treated cases in 1955 suggested the use of local infiltration anesthesia (0.5 per cent procaine) in the acutely ill infant, supplemented by sedation given with a gauze nipple saturated with a 1 to 3 mixture of brandy and 10 per cent glucose in water. Amadeo (37) also considers local infiltration anesthesia as the safest in the acutely ill premature infant. Linkner and Benson (75) who reported a series of 13 surgically treated cases prefer general endotracheal anesthesia. In 53 instances the type of anesthesia was not recorded.

Type of incision: Table XIII shows the various types of incision employed. Linkner and Benson (75) used a right paramedian and, less frequently, an upper midline incision. Although experienced pediatric surgeons can reach any part of the abdomen through a right paramedian incision, adequate exposure of the entire stomach and, particularly, the esophagogastric junction can be provided easier by an upper midline incision. In 3 instances (22, 38, 62), the original low placed incision had to be extended proximally to provide adequate

TABLE XII
Type of Anesthesia

	No. of Cases
Local	20
General	30
Not Recorded	53
	103

TABLE XIII
Type of Incision

	No. of Cases
Upper Abdominal	7
Upper Abdominal, Midline	3
Upper Abdominal, Transverse	6
Upper Abdominal, Subcostal	1
Right Paramedian*	14
Left Paramedian	2
Lower Abdominal, Midline	2
Not Recorded	55
	90

* In the 13 cases of Linkner and Benson a right paramedian and less frequently an upper midline incision was used.

exposure of the fundus of the stomach where the majority of perforations are located.

Exploration: The high incidence of perforation in the fundic half of the stomach and particularly the region of the cardia is shown in Table XIV. A predilection for the greater curvature aspect of the stomach is also demonstrated.

The opening of the lesser sac and inspection of the posterior wall of the stomach has been emphasized repeatedly. Among 8 cases (5, 9, 13, 14, 18, 53, 75) in which the primary or a second perforation was overlooked at operation, the autopsy revealed a perforation of the posterior wall in 4 instances (5, 9, 14, 75).

Detailed exploration of the remainder of the gastrointestinal tract to rule out distal obstruction is necessary.

Repair: After excision of the necrotic edges at the site of perforation (the size

ranged from 1 mm to 4.5 cm), the repair is carried out in two layers; the first with a through-and-through chromic catgut and the second layer consisting of inverting interrupted seromuscular sutures. Inadequate closure of the site of perforation may lead to dehiscence and reperforation. Resection of a segment of the stomach because of the size of perforation was necessary in 3 instances (17, 41, 75). In one case (75), the site of perforation was sealed at the time of operation and repair was unnecessary. Instillation of warm sterile saline solution into the stomach through a nasogastric tube to prove the integrity of the closure and detect other perforations or distal obstruction may be desirable. Full-thickness gastric biopsies from the site of perforation, prior to repair, are important for diagnostic and investigative documentation.

Tube gastrostomy: In order to effectively decompress the stomach and prevent regurgitation of gastrointestinal contents and minimize the possibility of aspiration, a tube gastrostomy, Carter-Stamm type, may be employed. This procedure

TABLE XIV
Site of Perforation

	No. of Cases
Fundus	64 (25 of these near cardia)
Midportion	13
Antrum	13
Pyloric Region	9
Greater Curvature	85
Lesser Curvature	26
Anterior Wall	49
Posterior Wall	17

was used only in 3 instances (37, 48, 79); in 2 cases, the perforation was closed around the tube, a procedure which resulted in leakage, peritonitis and death (37, 79). In the vast majority of cases, a nasogastric tube was used and proved to be adequate.

Duodenojejunostomy for obstruction of duodenum by the superior mesenteric vessels was necessary in one case (48). A high feeding jejunostomy was used in only one instance (11).

Closure of the abdomen: In most instances the abdomen was closed without drainage. Whenever a localized abscess was found, drainage was employed.

Postoperative care: Intravenous fluids have been used until oral feedings could be instituted. Nasogastric suction was maintained, usually from 48 to 72 hours, until peristaltic activity was heard on auscultation of the abdomen. Antibiotics were employed pre- and postoperatively.

MORTALITY RATE

The overall mortality was 75.47 per cent (Table I). With the exception of one survivor, the mortality in the nonoperated group was 100 per cent. Of the 103

surgically treated cases, 38 or 36.89 per cent survived (Table XV). While the rate of prenatal maternal complications was not unusually high, the incidence of associated congenital anomalies was higher than one would expect. In the broad spectrum of the recorded congenital anomalies, the gastrointestinal tract is represented with a significant number of abnormalities, particularly of the atretic or stenotic variety (Table XVI). The mortality rate among the operated premature infants was higher than in the group of mature babies (Table XV). The survival rate of male infants was smaller than in their female counterparts of the surgically treated group. Among the prematurely born children the ratio of survival with operation was one boy to three girls.

The major cause of death in the majority of cases was generalized peritonitis. Septicemia may have accounted for the death of 5 children (31, 53, 54, 78). In one instance (55) a phlegmon of the stomach was considered part of a generalized septic process. The associated congenital anomalies may to a certain extent have contributed to the mortality of these children.

TABLE XV
Mortality in Surgically Treated Cases

Survived	38	→Premature	15
		→Full-term	14
		→Weight not recorded	9
Died	65	→Premature	31
		→Full-term	17
		→Weight not recorded	17

CASE REPORTS

Case 1. Baby Girl B. (195876) was born June 10, 1962, prematurely at 34 to 35 weeks of gestation and weighed 2100 grams (4 lb. 10 oz.).

The mother, a healthy 22-year-old Negro primigravida, had had an uneventful pregnancy. Her serologic test for syphilis was negative. The membranes ruptured three days before the spontaneous delivery; she received oral tetracycline during the three days prior to hospitalization and upon admission to the hospital she was given intramuscular antibiotics. The rectal temperature was 100.8° F. on admission.

After 7 hours and 15 minutes of labor the child was delivered as a vertex presentation. The infant breathed and cried immediately after delivery. Suction was carried out and oxygen was administered.

The infant was taken to the premature nursery where physical examination revealed acrocyanosis, grunting respirations, and intercostal retractions. A few rales were heard over the right lower lung field posteriorly and the possibility of a neonatal pneumonia was considered. The child was placed in an isolette, oxygen in a concentration of 34 to 38 per cent was administered and antibiotic therapy in the form of parenteral neomycin was instituted.

During the first day of life subsidence of the respiratory distress was noted. Intramuscular penicillin was added to the antibiotic regimen. Oral feedings were started approximately 48 hours after birth and were tolerated well. Passage of meconium and transitional stools was normal. Slight icterus was noted on the second day of life. On the fifth day the child became listless, moderately icteric and refused feedings. Progressive abdominal distention and bilious vomiting persisted throughout the fifth and sixth day of life. Bowel sounds were absent.

TABLE XVI
Associated Congenital Anomalies

System	No. of Cases
Gastrointestinal	
Esophageal atresia	1
Pyloric atresia	1
Circular constriction of stomach	1
Duodenal atresia	3
Malrotation of the intestine with band constricting the duodenum	3
Congenital stenosis of duodenum	2
Obstruction of duodenum by superior mesenteric vessels	1
Meckel's diverticulum with small adhesive band	1
Meconium ileus	1
Obstruction of ileocecal valve	3
Narrowing of rectum	1
Multiple areas of fibrosis in stomach, liver, pancreas and spleen	1
Genitourinary	
Bilateral hydronephrosis	1
Bilateral hypoplasia of kidneys	1
Multiple cysts of right kidney	1
Atresia of left ureter with multicystic kidney	1
Ureteral ectasia without obstruction	1
Multiple abnormalities of urethra, bladder, ureters (kidneys small, histologically defective)	1
Dilatation of the bladder requiring cystostomy	1
Cryptorchidism	1
Cardiovascular	
Infantile coarctation of the aorta with cardiomegaly	1
Respiratory	
Severe atelectasis of both lungs	1
Tracheo-esophageal fistula	1
Central Nervous System	
Intracranial hemorrhage	3
Internal hydrocephalus	1
Spina bifida with myelocoele	1
Spina bifida with meningocele	1
Arches and Face	
Hare lip, cleft palate	1
Musculoskeletal	
Diaphragmatic hernia	2
Skin	
Multiple hemangiomas of skin with areas of hyperpigmentation	1
Miscellaneous	
Mongolism	1
Mongoloid appearance	2
Microphthalmia with congenital toxoplasmosis	1
Omphalocele, ruptured	1
Gangrene of left foot	1

Introduction of a nasogastric polyethylene tube yielded a small amount of greenish mucoid material. Oral feedings were discontinued and the child was given intravenous fluids and Chloromycetin. A small amount of blood, passed per rectum, was attributed to an anal fissure. In the morning of the sixth day x-rays of the abdomen in supine position revealed a diminution of the normally seen intestinal gas pattern (Fig. 2). In the afternoon of the same day the child was seen in consultation by the pediatric surgical service. The most significant findings were confined to the abdomen, which was soft but moderately distended. Bowel sounds were absent. An intestinal obstruction was suspected and further x-ray studies were

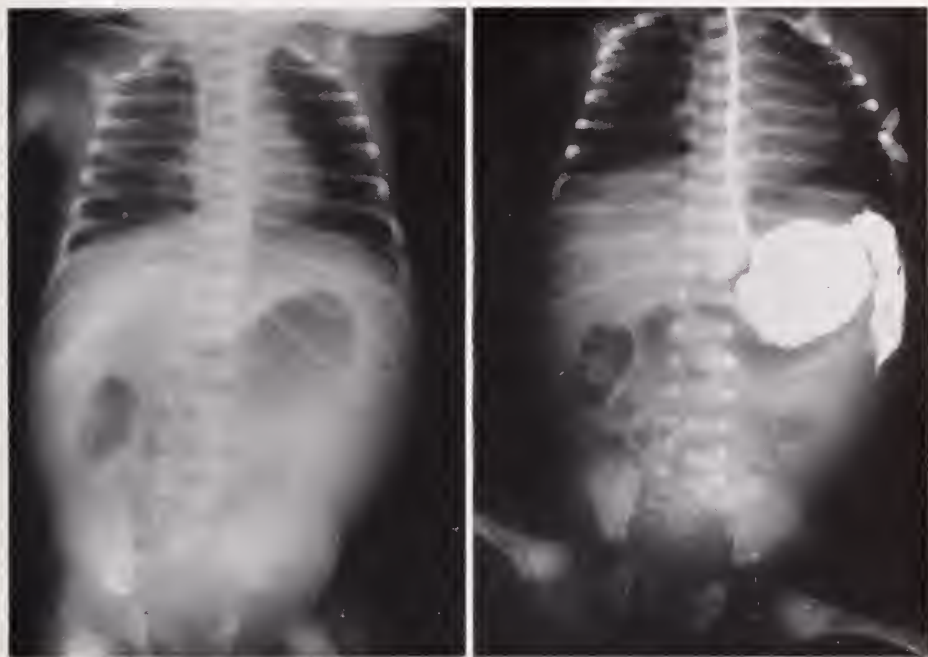


FIG. 2. (Left) Plain film of the abdomen in supine position, revealing a diminished intestinal gas pattern. An air shadow over the mid-epigastrium, suggesting free air in the peritoneal cavity, can be recognized with difficulty.

FIG. 3. (Right) Upper gastrointestinal study with diatrizoate methylglucamine, showing the perforation of the fundus of the stomach. Note the nasogastric tube in the esophagus and the free air under the diaphragms.

done. Multiple films of the abdomen were taken in prone, supine and upright positions following injection of Gastrografin (diatrizoate methylglucamine) through a nasogastric tube. A perforation in the fundus of the stomach with tracking of the contrast material down the left lateral gutter in the free peritoneal cavity was demonstrated radiographically. Free air under both diaphragms was noted (Fig. 3). Re-examination of the previously taken scout films in supine position showed that free air could be recognized with some difficulty on these films (Fig. 2).

Abdominal exploration under local anesthesia (Xylocaine 0.5 per cent) through a midline upper abdominal incision revealed a moderate amount of gas and greenish (biliary) material in the free peritoneal cavity. There was evidence of generalized peritonitis. In the region of the anterior wall of the fundus of the stomach on the greater curvature side a perforation was found measuring approximately 1.5 cm in length. Surrounding this perforation was an ellipti-

cal seromuscular defect of approximately 5 cm in length and 2 cm in width. A biopsy was taken from the edge of the site of perforation.

The perforation was closed with a continuous chromic catgut suture. The seromuscular layer was then reapproximated with interrupted silk sutures (Fig. 4). A Carter-Stamm type tube gastrostomy was constructed and the abdomen closed using stainless steel wire for the peritoneum and fascia, and silk for the skin.

The child tolerated the procedure very well.

OPERATIVE FINDINGS & MODE OF REPAIR

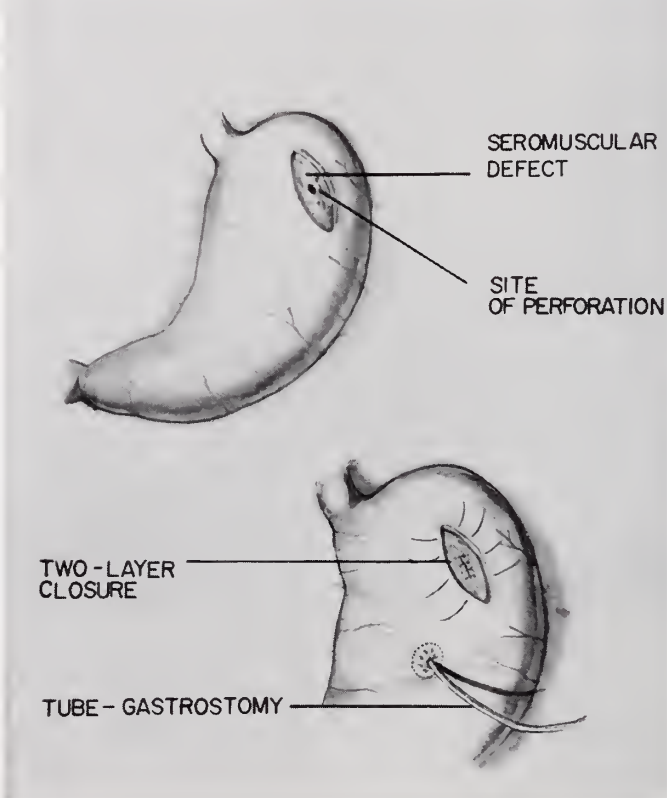


FIG. 4. Anterior view of the stomach, showing site of perforation and mode of repair.

The postoperative course was characterized by intermittent vomiting, abdominal distention and diarrhea. Repeated Gastrografin and barium studies of the gastrointestinal tract failed to reveal any intrinsic or extrinsic abnormality. On the thirteenth postoperative day, *E. coli* (type 0119B14) was cultured from the stool. Neomycin 50 mg per kg body weight per day was given via the gastrostomy tube. On the nineteenth postoperative day, a marked drop of the hemoglobin down to 5.4 Gm% was noted and multiple whole blood transfusions were given to restore the blood volume to normal levels.

A slow but progressive improvement of the child's condition followed. The diarrhea subsided and the stool cultures became negative for enteropathogenic organisms. The baby gained weight gradually and left the hospital on the thirty-first postoperative day with a weight of 2400 grams.

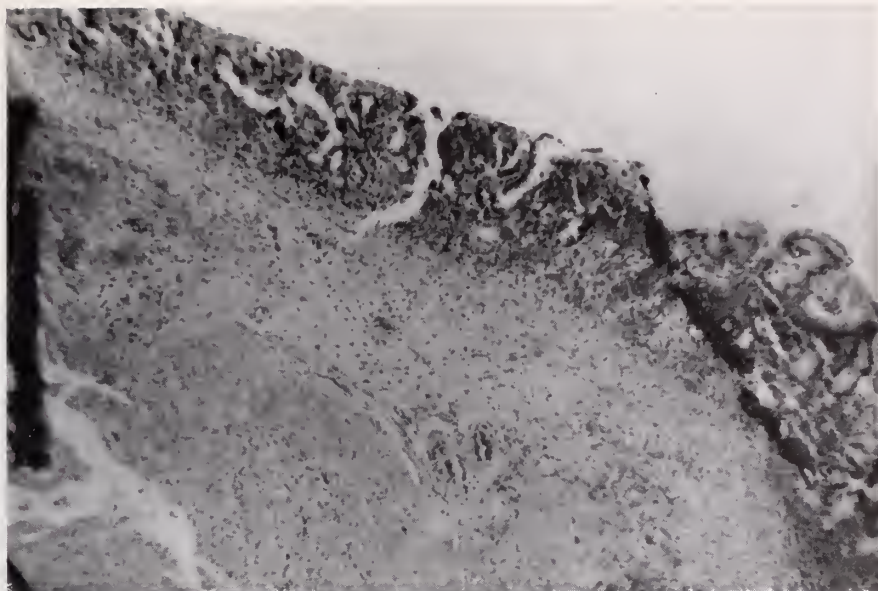


FIG. 5. Low-power photomicrograph of the biopsy specimen taken from the edge of perforation of the stomach ($\times 10$). Note the acute and chronic nonspecific inflammation and the absence of muscle fibers.

Biopsy taken from the edge of perforation was reported: (S.S. 148371) "Fragment of gastric mucosa showing necrosis with acute nonspecific inflammation. No external muscularis included in specimen" (Fig. 5). Ten months after the operation the baby is doing well and weighs 16 pounds and 13 ounces.

Case 2. Baby Girl G. (205697) was born at another hospital on November 2, 1962, at 36 weeks of gestation, weighing 3 lbs. 12 oz.; she was one of twins. The mother was a healthy Puerto Rican, para 1001, who had an uneventful pregnancy. Her serologic test for syphilis was negative and her blood group was A, Rh positive.

After 58 minutes of labor a precipitous delivery from the L.O.A. position was carried out. The child breathed and cried spontaneously and the condition at birth was described as good. Oxygen was administered; no stimulants were used and vitamin K was given parenterally. The child was placed in an incubator.

Seven hours after birth the child was transferred to the premature nursery of our institution where physical examination revealed an essentially normal premature infant except for deviation of the nose to the right. During the first five days of life the child took the feedings well. The temperature ranged from 96.4° to 98.8° F. Passage of meconium and transitional stools was normal. On the morning of the sixth day of life, the baby fed very poorly and became lethargic; perioral cyanosis and mild icterus were noted. The pulse rate was 160 per minute, the cry became weak and the child responded only to painful stimuli. The possibility of intracranial hemorrhage or sepsis was considered. Cultures of blood, umbilicus and nasopharynx were taken and antibiotic therapy with penicillin and neomycin was instituted.

Abdominal distention persisted; periumbilical erythema was noted and the umbilicus was considered the portal of entry for possible septicemia. The infant was icteric with a bilirubin of 12.4 mg %. A lumbar puncture yielded a normal spinal fluid. On the evening of the sixth day of life a constipated stool was passed. Approximately twenty-four hours after

the blood culture was taken *b*-hemolytic *Streptococcus* grew out in all media. The same organism was cultured from the umbilicus and nasopharynx. During the seventh day of life the baby took the feedings well. However, abdominal distention persisted. Absence of bowel sounds was noted as well as guarding in the region of the hypogastrium.

Because of persisting signs of peritonitis, x-rays of the abdomen in supine and upright positions were taken which revealed the presence of free air under the diaphragms (Fig. 6). The roentgenograms showed air in the stomach and in the small and large bowel. With the preoperative diagnosis of a perforated viscus (small bowel or stomach), the child was subjected to an exploratory laparotomy under local infiltration anesthesia (Xylocaine 0.5 per cent).

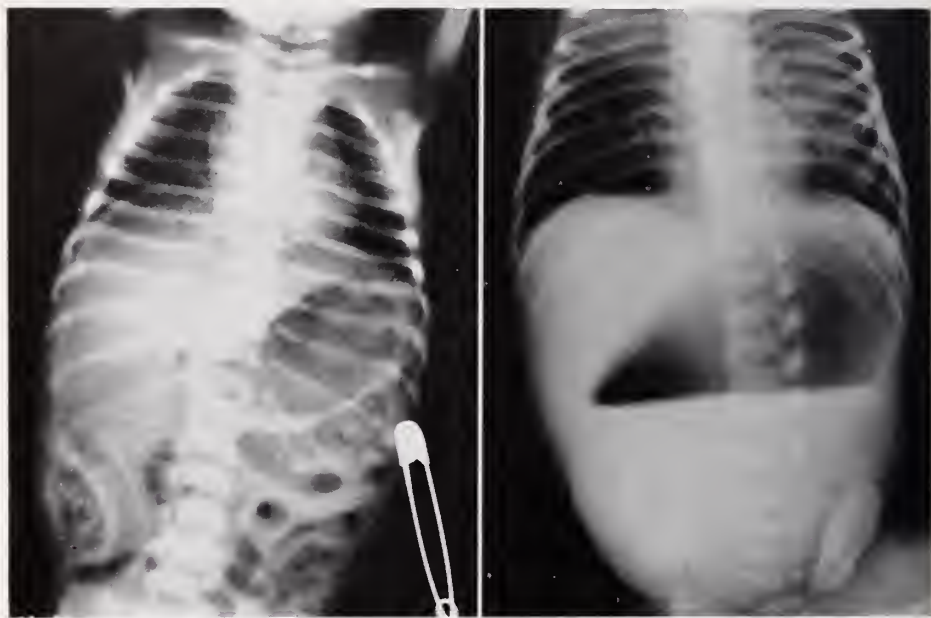


FIG. 6. (Left) Scout film of the abdomen in upright position revealing free air in the peritoneal cavity particularly under the right leaf of the diaphragm.

FIG. 7. (Right) Preoperative scout film of the abdomen showing a markedly distended stomach and a large air-fluid level. Note the minimal amount of gas beyond the pylorus.

The abdominal exploration was carried out through a midline upper abdominal incision. Upon opening the peritoneal cavity, air escaped. A localized peritonitis was found in the region of the right lower quadrant, where a small amount of purulent exudate was seen; a culture was taken from this region and grew out *Aerobacter aerogenes* and *Staphylococcus aureus*. In spite of thorough exploration of the stomach, small and large bowel, the site of perforation was not ascertained. The abdomen was closed without drainage. The child received 15 cc of blood during and immediately after the operation. Nasogastric suction was maintained for approximately 72 hours when peristaltic activity and bowel function returned to normal. Intravenous fluids were given until oral feedings were well tolerated. The antibiotic therapy with penicillin and neomycin was continued during the immediate postoperative period and substituted by Staphicillin on the eighth postoperative day. The abdominal wound healed by primary intention. A moniliasis of the lips and tongue was controlled by administration of Mycostatin. The infant's postoperative course was other-

wise uneventful. The child was discharged 37 days after the operation with a weight of 2370 grams. Six weeks after the operation the infant was readmitted here with a pneumonia of the right lower lobe. Three months after the operation the baby was in good health, weighing 8 pounds and 10 ounces.

Case 3. This Puerto Rican female infant (93155) was born at the Beth Israel Hospital, New York, on February 12, 1963, after a normal spontaneous delivery. The birth weight was 5 pounds and 12 ounces. There was no evidence of fetal distress or anoxia and no resus-



FIG. 8. Preoperative upper gastrointestinal study with diatrizoate methylglucamine showing retention of the dye in the stomach. The herniated mucosal pouch is visible (outline designated by arrows).

citative measures were employed. Initially the infant tolerated glucose and water feedings and passed meconium stools. On the second day of life the baby vomited coffee ground material and on the third day abdominal distention occurred. Plain x-ray films of the abdomen revealed marked distention of the stomach with a large air-fluid level. Minimal amount of gas was seen beyond the pylorus (Fig. 7). Contrast studies with diatrizoate methylglucamine (Gastrografin) showed retention of the dye in the stomach (Fig. 8).

The baby was taken to the operating room with a preoperative diagnosis of congenital obstruction in the region of the pylorus. The abdominal wall was infiltrated with 0.5 per cent procaine and a transverse incision, one fingerbreadth above the umbilicus was carried out. A small amount of bloody fluid was found in the peritoneal cavity. There was a long seromuscular tear in the anterior wall of the stomach close to the greater curvature, ex-

tending from the pyloric region to the fundus. Dilated mucosa herniated through this defect creating a pocket three times the size of the stomach itself (Fig. 9). The herniated mucosa was replaced into the lumen of the stomach and the defect was repaired with interrupted seromuscular sutures of No. 4-0 silk, except for the most cephalad portion where the overlying left lobe of the liver and the spleen made the repair technically impossible (Fig. 10). The omentum was tacked up to cover the suture line.

The remainder of the abdominal cavity was then explored. Malrotation of the intestine was found with the cecum in the right upper quadrant. Ladd's bands crossed the duodenum

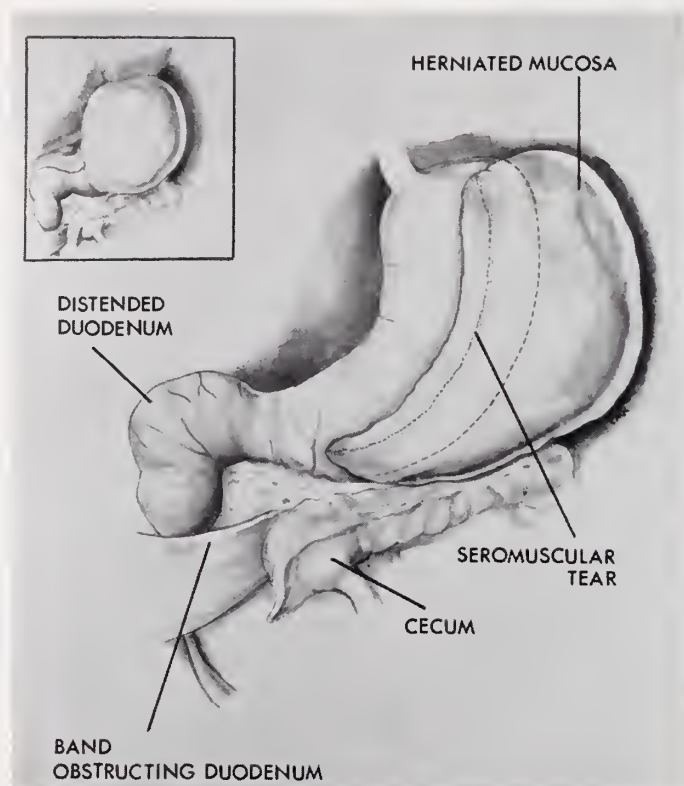


FIG. 9. Anterior view of the abdominal situs, showing herniation of gastric mucosa through a seromuscular tear, and malrotation of the intestine with band obstructing the duodenum. Note the size of the mucosal herniation in relation to the stomach (insert).

partially obstructing it. The proximal duodenum was dilated. After division of Ladd's bands, the duodenum was noted to descend to the right lower quadrant to the right of the superior mesenteric artery (Fig. 10).

An opening was made in the posterior wall of the body of the stomach within a purse string suture of No. 3-0 chromic catgut. A rubber catheter was passed through the pylorus and duodenum and into the jejunum to rule out intrinsic obstruction. This catheter was then removed and replaced with a No. 5 French polyethylene catheter threaded 8 inches into the jejunum. A No. 14 Foley catheter was passed through the same opening in the stomach (Fig. 10). The balloon was inflated with 3 cc of saline and the purse string was tied. A stab wound was made through the left rectus muscle above the incision and both catheters were brought out through this wound. The stomach was then sutured to the anterior abdominal wall.

The abdominal wall was closed with wire for peritoneum and fascia, and silk for skin closure.

Postoperatively, the gastrostomy tube was kept on gravity drainage and the baby was fed intravenously. After 48 hours, the gastric drainage was instilled into the jejunostomy tube every two hours. On the fourth postoperative day, clear fluids and on the fifth postoperative day dilute formula were instilled into the jejunostomy tube. By the sixth postoperative day the baby was on full-strength formula.

Her weight fell slowly, reaching a low point of 4 pounds, 9 ounces on March 3, 1963. At this

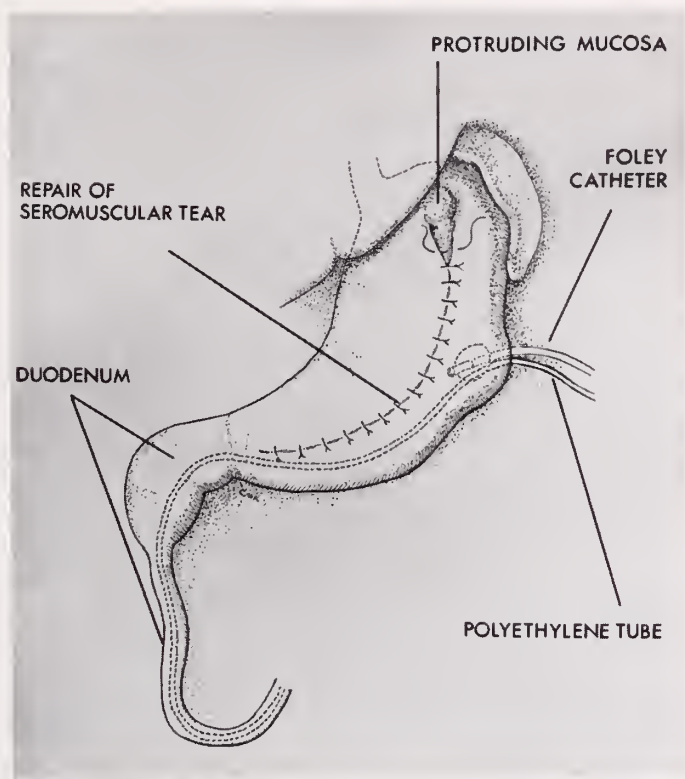


FIG. 10. Repair of the seromuscular tear after replacement of the mucosa into the stomach. The repair of the proximal end of the tear was technically impossible (lying under the spleen and left lobe of the liver).

Note the abnormal course of the duodenum after division of the obstructing band. Foley catheter acting as gastrostomy. Polyethylene tube acting as feeding jejunostomy.

time the jejunal tube was removed. Feedings continued through the gastrostomy tube for another 48 hours. The gastrostomy tube was then removed, and increasing feedings were given by mouth.

The infant began to gain weight and was discharged on March 16, 1963, weighing 5 pounds, 6 ounces.

DISCUSSION

Perforation of the stomach in the neonatal period is far from rare. In a review of the literature we found 159 cases reported since 1826. Reviews of the literature were presented by Vargas *et al.* (31) in 1955 and Hallaba *et al.*

(41) in 1961. Our own experience is limited to three cases: One case of gastric perforation, one infant with pneumoperitoneum of undetermined origin and a case of seromuscular tear of the stomach with herniation of the mucosa and impending rupture. All three infants exhibited similar clinical pictures, were operated upon and survived.

The uniformity of the clinical picture with the sudden onset of illness limited primarily to the first week of life should arouse suspicion for the possibility of gastric perforation. The demonstration of pneumoperitoneum on the scout film (upright position) constitutes the prime indication for an immediate exploratory laparotomy. In doubtful cases roentgenographic study of the upper gastrointestinal tract with the aid of a contrast medium may be of extreme help in establishing the diagnosis or delineating the site of perforation. A water soluble medium should be used rather than opaque oil or barium; the substance may be given in a milk bottle or injected through a nasogastric tube. It has been clearly shown that the mortality is directly proportional to the length of time which elapses between the onset of symptoms and the time of surgical intervention. The exploration can be performed under local infiltration anesthesia in the premature acutely ill infant.

If gastric perforation is suspected or diagnosed preoperatively, an upper mid-line incision should be employed to provide adequate exposure of the fundus and cardia of the stomach, a region most frequently affected by rupture in the neonatal period; the posterior wall of the stomach should be routinely inspected by opening the lesser peritoneal sac. Adequate closure by placing the sutures through healthy tissue will prevent dehiscence of the wound or extension of the perforation. A thorough inspection of the distal gastrointestinal tract should be made prior to closure. If a tube gastrostomy is done, the tube should not be brought through the site of perforation; the necrotic edges do not provide suitable tissue for a tight closure around the tube.

Tunger (85) in 1936 reported a case of spontaneous pneumoperitoneum in a newborn infant with complete resolution of the process within eighteen days while surgical intervention was deferred.

A similar case was reported by Steinberg (86): a one day old infant developed abdominal distention, and pneumoperitoneum was demonstrated radiographically. The child survived without operation. On the tenth day of life an acute, necrotizing orchitis necessitated unilateral orchidectomy, a procedure well tolerated by the infant, who left the hospital on the fifteenth day.*

Linkner and Benson (75) described a case where the small gastric perforation was sealed at the time of operation, and, consequently, repair was not necessary. Our second case of pneumoperitoneum, though obscure, probably represents an unrecognized lesion similar to that of Linker and Benson. Both infants survived and would have survived without operation. In spite of these examples, surgical intervention remains the therapy of choice in this condition. There was only one survivor among the 56 nonoperated cases of gastric perforation, and of the 103

* By permission of Dr. D. Steinberg who reported this case at the February 1963 meeting of the Bronx Pediatric Society, New York, N. Y.

infants treated surgically, only 38 survived. This high mortality may be partially attributed to the multiplicity of other associated congenital anomalies or septicemia. However, the delay in performing an exploratory laparotomy with the invariable result of death due to peritonitis remains a basic factor in the high rate of mortality.

Etiology and Pathogenesis

The etiology and pathogenesis of this disease remains obscure. Until 1943 perforation of the stomach in the newborn period was attributed to acute or chronic peptic ulcer. In 1919 Theile (87) presented a collective review of ulcerations of the gastroduodenal tract in children. He found 119 cases of gastric ulcer, 34 of which occurred in the neonatal period with perforation in 7 instances.

Bird and his associates (88) in 1941 collected 243 cases of peptic ulceration of the stomach and duodenum in infants and children. Of these, 38 were found in the newborn period with gastric localization in 12 cases and duodenal or pyloric in 26 instances; 5 of these 38 infants developed perforation and were operated upon with one survivor.

In 1941 Miller (89) studied the gastric acidity during the first month of life. He found a high degree of acidity during the first 48 hours, comparable to that of a healthy adult; after the second day the free acid falls to zero in most cases. A gradual rise occurs after the tenth day. He assumed that a gastrogenic hormone transmitted to the infant from the mother or placenta accounts for the high acidity during the first 2 days. Recent investigations of gastric acidity in premature infants by Ames (90) show no significant fluctuation of the acid levels during the first 10 days of life.

Herbut (21) in 1943 introduced the concept of a "congenital muscular deficiency" as the cause of gastric perforation in the neonatal period. This concept was based on the embryological differentiation of the gastric musculature as described in the fundamental work of Plenk (91).

The anlage for the circular muscle layer appears as a thickening of the mesenchyme along the distal end of the esophagus and the lesser curvature of the stomach. Similar mesenchymal thickenings in the fundic and greater curvature regions appear at a later embryonal stage. The longitudinal muscular layer appears later and is always very thin; it may be partially absent even at birth. Herbut postulated that failure in the growth of the muscle cells from the anlage on the lesser curvature or a poor development or absence of the mesenchymal islands in the fundus and greater curvature may lead to congenital defects in the wall of the stomach.

Herbut's concept of mesenchymal deficiency, which found acceptance in textbooks of pathology (25, 92), is purely hypothetical. Abnormal thinning of the gastric wall or microscopic absence of muscle fibers can be produced by overdistention of the stomach (pneumatic pressure, distal obstruction) and are not dependable criteria for a defective development of the gastric musculature (51). The localization of the majority of gastric perforations in the fundus along the greater curvature is not pathognomonic of defective musculature. Sufficiently

high doses of histamine given to animals will produce ulcerations and perforations almost exclusively in the region of the fundus of the stomach (93).

The occurrence of gastric diverticula with predilection for the greater curvature may be related to the penetration of this region by vascular trunks, a phenomenon comparable to that seen in diverticulosis (51).

If deficient muscle were the cause of gastric perforation one would expect a much higher incidence of rupture following Fredet-Ramstedt pyloromyotomy.

Musser (51) emphasized the importance of gastric distention produced by mechanical resuscitation and felt that the incidence of gastric perforation runs parallel to the therapeutic use of oxygen under pressure. Most likely, the dilatation of the stomach due to distal obstruction also represents a significant element in the genesis of gastric perforation.

If we accept the theory of "congenital muscle defect" without criticism, we ignore elementary factors which come into play during the first few days of the infant's life: the high gastric acidity during the first 48 hours (89) in an organ which is not prepared for such high peptic activity; the overdistention of the stomach due to exogenous (mechanical resuscitation) or intrinsic (distal obstruction) causes. Our third case emphasizes the significance of distal obstruction as a cause of gastric perforation.

Although well documented in few instances, it is difficult to believe that tube trauma alone can produce perforation in a normal stomach. It is more likely that peptic or mechanical alterations of the gastric wall precede the trauma due to intubation.

Wagner *et al.* (94) emphasized the precautions to be taken when frequent insertion of polyethylene tubes for feeding of premature infants is necessary. The association of septicemia and perforation of the stomach was recorded in 5 instances (31, 53, 54, 78). In the case of Gerasimenko (55), a phlegmon of the stomach was considered the cause of perforation. Multiple ulcerations and/or perforations are suggestive of septicemia (57).

The theory of neurogenic origin of peptic ulcers introduced by Rokitansky was revived in the time of Cushing (95), who stressed the occurrence of ulcerative and perforative lesions of the gastrointestinal tract following surgical intervention for cerebellar tumors or other intracranial lesions. Davis and his associates (96) in 1955 studied the correlation between upper alimentary tract lesions and neurosurgical operations and came to the conclusion that gastrointestinal ulcerations and hemorrhages are the result of stress due to surgery, regardless of its location.

The majority of the authors agree that birth trauma alone is unlikely to cause gastric perforation.

CONCLUSIONS

1. Sudden onset of abdominal distention in a newborn infant, particularly during the first week of life, must draw the physician's attention toward the possibility of a gastric perforation.

2. Labored respirations and cyanosis often precede or accompany abdominal

distention and should not mislead the clinician towards incorrect diagnoses of pulmonary or cardiac disease.

3. Plain films of the abdomen and chest must be taken in the upright position, even if the suspected illness is cardiac or pulmonary in nature. Absence of the normal gastric air bubble is suggestive of gastric perforation. In doubtful cases contrast media should be used, preferably water soluble media, in order to obtain a precise roentgenologic diagnosis.

4. Once the diagnosis of gastric perforation is established or suspected, exploration of the abdomen through a midline upper abdominal incision should be carried out; local infiltration anesthesia may be used in the desperately ill premature infant. The fundus of the stomach, the region of the cardia and the posterior wall of the stomach must be inspected thoroughly; if the perforation is found and repaired, exploration of the distal gastrointestinal tract is necessary to avoid overlooking distal obstruction.

5. A tube gastrotomy is advisable; the tube should be introduced into the stomach through a separate gastrotomy within the healthy portion of the anterior wall of the stomach.

6. Full thickness gastric biopsies should be taken and may be of great value in determining the etiology of the perforation.

7. The use of pre- and postoperative antibiotics is indicated.

8. Attention is drawn to the need for gentle and careful use of mechanical resuscitators and nasogastric tubes.

9. Further studies to elucidate the nature of this entity are necessary. Distal obstruction and mechanical resuscitation producing overdistention of the stomach are important factors.

SUMMARY

Significant data from 159 case reports of neonatal gastric perforation have been collected. The case records of three surgically treated infants with survival are presented. The etiology and pathogenesis of this entity are discussed.

Precise knowledge of the disease and prompt surgical intervention will yield more fruitful results in the future. Expectant treatment is completely unjustified. Without operation the mortality is almost 100 per cent.

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Stool Water Content in the Neonatal Period

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It is known that stools of newborn babies vary considerably in frequency (1) but few studies have emphasized the variability of their consistency. This study was undertaken to determine the percentage of water of individual stools in the neonatal period of babies on different feeding regimens.* We were unable to consider the number and amount of stools passed and therefore we did not determine the daily total water loss in the infants' stools.

MATERIALS AND METHODS

Newborn babies in this hospital's regular nurseries receive nothing by mouth for the first twelve hours, after which they are gradually fed increasing amounts of 5% glucose in water. At twenty-four hours of age the bottle-fed babies are fed a diluted formula containing 45 calories/100 ml (13½ calories/oz) at 4 hour intervals. This concentration is designated as Formula No. 1.

Formula No. 2 containing 67 calories/100 ml (20 calories/oz) is begun on the fifth day of life.

For the purpose of this study, some bottle-fed babies weighing less than 3300 grams at birth were continued on the more dilute Formula No. 1 until the time of their discharge, usually between the fifth and the eighth day of life.

Breast-fed babies were fed at similar time intervals; they received supplementary feedings of 5% glucose in water and no formula.

Bottles were sterilized by terminal autoclaving at 8 pounds pressure for 10 minutes at 240°F during the initial period of our study. During the last two years the autoclave has been regulated at 6 pounds pressure for 10 minutes at 230°F.

The stools were collected between 10 A.M. and 2 P.M. on special plastic diapers† to exclude urine, and for the same reason only male babies were studied. The stools were transferred to previously dried and weighed evaporating dishes; each stool in its evaporating dish was weighed again and then placed in an oven. The oven's temperature was kept between 100°C and 104°C. Two days later the dish plus stool was weighed, after previous cooling in a calcium chloride desiccator, and returned to the drying oven. This procedure was repeated daily until constant weight was reached on two consecutive days. The usual time required was four to five days. The percentage of water lost was then calculated.

For each group the mean, standard error of the mean, and standard deviation were calculated. Statistical analysis was performed to determine whether significant differences exist between the means of comparable groups ("t"

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† Tomac urine specimen diapers made by American Hospital Supply Corporation, Evanston, Illinois.

TABLE I
Composition of Feeding (67 Calories/100 ml—20 Calories/oz)

Nutrient	B	P	R	V	W	X
<i>Composition w/v</i>						
Protein	1.2	2.7	3.24	1.72	1.5	2.35
Fat	3.8	2.8	2.66	3.4	3.7	3.0
Carbohydrate	7.2	7.75	7.68	6.55	7.3	7.75
<i>Caloric Distribution %</i>						
Protein	7	16	14.3	11	9	14
Fat	51	38	35.9	48	50	40
Carbohydrate	42	46	49.8	41	41	46
<i>Type of:</i>						
Fat	Breast milk fat	Butterfat	Butterfat	Blend of corn, coconut, olive oils	Blend of oleo, corn, coconut oils	Blend of corn, coconut, olive oils
Carbohydrate	Lactose	Lac. + D.M.	Lac. + D.M.	Lactose	Lactose	Lac. + D.M.
Lactalbumin: Casein	1.6-1.7/1	1/7	1/6	12/85	1/7	1/7
Calcium: Phosphorus	2.2/1	1.3/1	1.27/1	1.3/1	1.3/1	1.3/1
Ash (%)	0.21	0.6	0.6	0.38	0.4	0.5

B—Breast milk

W—Simulated breast milk, different brand

P—Carbohydrate-modified cow's milk formula

X—Formula with intermediate fat and protein content

R—Evaporated milk, dextri-maltose formula

V—Simulated breast milk

Lac. + D.M.—Lactose + dextri-maltose

value) (2, 3). For our purpose we have considered "significant" any "t" values above 3 (probability of 370:1).

Stools from the following groups were studied:

1. Meconium stools mostly from babies approximately 24 hours old. Meconium stools up to 72 hours of age were studied; they represented the first, second or third stools passed.

2. Breast-fed babies between 3 and 8 days of age; subsequently this group was divided into two groups: babies 3 or 4 days old and babies 5 days of age and older.

Artificially fed babies were divided according to age and formula concentration used.

3. Babies 3 to 4 days of age fed Formula No. 1.

4. Babies 5 to 7 days of age weighing less than 3300 grams at birth fed Formula No. 1.

5. Babies 5 to 8 days of age weighing over 3300 grams at birth fed Formula No. 2.

The following milk preparations were used:

P—Carbohydrate-modified cow's milk formula

Q—Same ingredients as P; flash sterilization

R—Evaporated milk formula with 5% dextri-maltose

V—Simulated breast milk

W—Simulated breast milk, different brand

X—Formula with intermediate fat and protein content

B—Breast milk

The composition of the various milk preparations are compared in Table I. The groups consisted of 50 to 70 samples of stool each.

RESULTS

Meconium stools were obtained within the first two days of life and were included if they "looked like meconium stools" and were one of the first two or three stools passed by the infant. The range, variation with age and distribution is shown in the scatter-graph (Fig. 1) and as can be seen no significant variation with age is apparent.

Breast-fed babies aged 3 to 8 days were studied in three experiments, months and years apart. The results obtained in the three experiments were statistically similar and were combined in Figures 1 and 2 and Tables II, III and IV*. The results were then divided into two groups according to the age of the babies, 3-4 days old and 5 days old and older. The stool water percentage and its relation to age is shown in the scatter-graphs (Figs. 1 and 2). A statistically significant fall in individual stool water percentage occurs after the fourth day.

Babies 3-4 days old were fed several artificial milk preparations in a concentration of 45 calories/100 ml (Formula No. 1). Statistical comparison between the means of the stool water per cent of the various feeding regimens was

* "t" value 3.56

made; although significant differences occurred no definite pattern was apparent (Fig. 1 and Table II).

Babies 5 days old and older fed Formula No. 1. The babies in this group weighed less than 3300 grams at birth. All the groups studied were smaller, only the first four products were studied and only "V" was studied twice. Figure 2 and Table III indicate wide variability in the water percentage of the individual stool. Breast and "V" stools show significantly lower water percentage than the stools from other preparations studied.

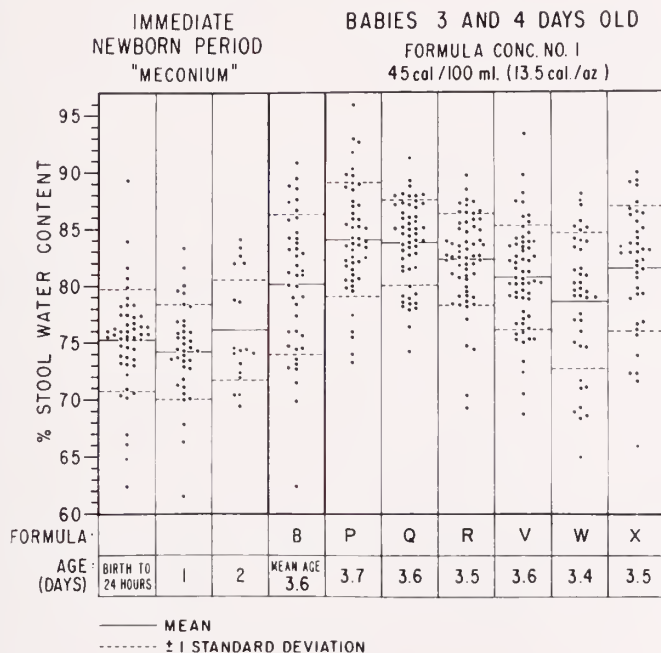


FIG. 1

B—Breast milk

P—Carbohydrate-modified cow's milk formula

Q—Same ingredients as P; flash sterilization

R—Evaporated milk, dextri-maltose formula

V—Simulated breast milk

W—Simulated breast milk, different brand

X—Formula with intermediate fat and protein content

Babies 5 days old and older were usually fed Formula No. 2. The babies were fed the six different preparations already described. The results are shown in Figure 2. Analysis of the results in Table IV shows that the breast-fed infants, and those receiving "V," "W" and "X" had lower water percentage in the individual stool than babies fed the other preparations, and that the difference is statistically significant.

FURTHER COMPARISONS

1. Individual stool water percentage from babies 3 and 4 days old fed Formula No. 1 was compared with that of babies on the same strength formula

TABLE II
Babies 3 to 4 Days Old
 Formula Conc. No. 1: 45 cal/100 ml (13.5 cal/oz)

Stool Water Results				Statistical Comparison ("t" Values)						
Mean Water Content-%	S.E.M.	St.D.		B	P	Q	R	V	W	X
80.17	0.96	6.13	B		3.31	3.20	1.83	0.38	1.21	0.94
84.11	0.71	4.94	P			0.52	2.20	3.82	4.75	2.46
83.66	0.51	3.72	Q				2.04	3.97	4.78	2.28
82.17	0.52	3.97	R					2.01	3.38	0.79
80.60	0.58	4.49	V						1.86	0.75
78.55	0.94	5.93	W							2.23
81.38	0.86	5.42	X							

S.E.M.—Standard error of the mean

St. D.—Standard deviation

B—Breast milk

P—Carbohydrate-modified cow's milk formula

Q—Same ingredients as P; flash sterilization

R—Evaporated milk, dextri-maltose formula

V—Simulated breast milk

W—Simulated breast milk, different brand

X—Formula with intermediate fat and protein content

$$\text{"t" values} = \frac{\text{Difference between means}}{\text{Standard error of difference}}$$

(probability values corresponding to 60 samples)

1.0	probability	2.15:1
2.0		21.:1
2.5		79.5:1
3.0		370.:1
3.5		2150.:1
4.0		15770.:1

TABLE III
Babies 5 to 7 Days Old
 Formula Conc. No. 1: 45 cal/100 ml (13.5 cal/oz)

Stool Water Results				Statistical Comparison ("t" Values)				
Mean Water Content-%	S.E.M.	St.D.		B	P	Q	R	V
75.53	0.61	4.08	B		8.65	9.61	11.28	2.44
84.70	0.87	3.46	P			1.30	0.03	6.01
82.93	0.47	2.60	Q				2.45	5.84
84.67	0.54	3.02	R					7.49
77.85	0.73	4.64	V					

S.E.M.—Standard error of the mean

St. D.—Standard deviation

B—Breast milk

P—Carbohydrate-modified cow's milk formula

Q—Same ingredients as P; flash sterilization

R—Evaporated milk, dextri-maltose formula

V—Simulated breast milk

For "t" values, see Table II

aged 5 days or older. (Figs. 1 and 2 and Tables II and III.) Only babies taking four of the products were studied, as well as the breast-fed babies in the same age groups. The statistical results are not shown; the only significant difference was in the water percentage of the individual stool of the breast-fed baby. As has been pointed out above, there is a marked decrease in stool-water per cent in breast-fed babies with the passage of time; from 80.17% in the 3-4 days old group to 75.53% in the older babies.

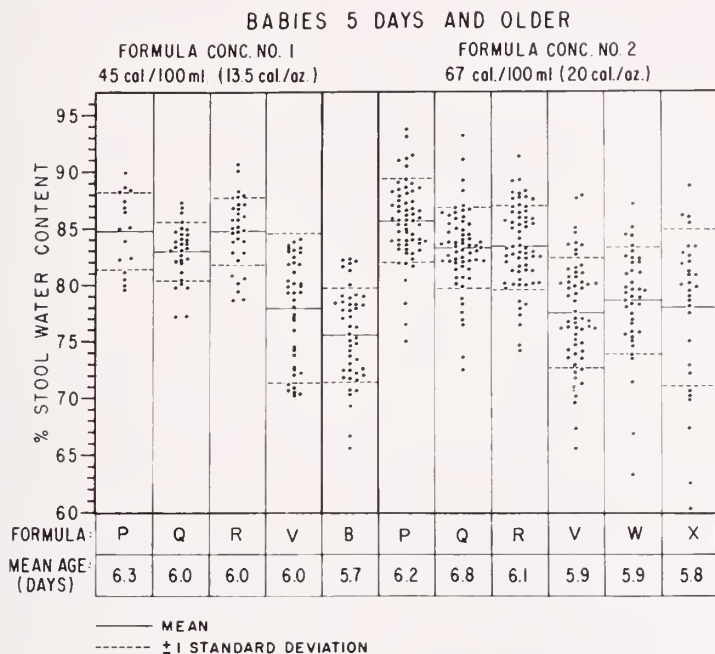


FIG. 2

P—Carbohydrate-modified cow's milk formula
 Q—Same ingredients as P; flash sterilization
 R—Evaporated milk, dextri-maltose formula
 V—Simulated breast milk

B—Breast milk
 W—Simulated breast milk, different brand
 X—Formula with intermediate fat and protein content

2. Individual stool water percentages were compared from babies 5 days old and older fed Formulas No. 1 and No. 2. Only the first four products listed were studied and no consistent difference or trend could be established. (Statistical results not shown.) (Fig. 2 and Tables III and IV.)

DISCUSSION

The purpose of this study was to determine the percentage of water of the individual stool in the first few days of life. The merit of the various feeding regimens was not under consideration nor were weight gain or weight loss analyzed.

Some general remarks about a stool study are in order.

Under hospital conditions, when diapers are changed only prior to and immediately after feedings, no accurate knowledge of stool frequency can be obtained. The extreme variability of stool number in the immediate newborn period has been discussed by Nyhan (1).

The relationship of the type of feeding and the amount fed to the stool number and total fecal water loss has not been recorded, although they are known to affect it (4). Levine *et al.* (5, 6) have shown that increased fluid intake results in increased urine without influencing stool water. In this study the average daily fluid intake of babies of the same age on various artificial milk preparations did not differ significantly.

TABLE IV
Babies 5 Days Old and Older
Formula Conc. No. 2: 67 cal/100 ml (20 cal/oz)

Stool Water Results			Statistical Comparison ("t" Values)							
Mean Water Content-%	S.E.M.	St.D.		B	P	Q	R	V	W	X
75.53	0.61	4.08	B		13.04	9.92	10.0	2.13	3.06	1.67
85.57	0.47	3.67	P			3.79	3.49	10.6	8.07	5.70
83.07	0.46	3.58	Q				0.24	7.39	5.23	3.88
83.23	0.48	3.78	R					7.50	5.35	3.97
77.38	0.62	4.78	V						0.96	0.35
78.47	0.75	4.73	W							0.41
77.87	1.26	6.89	X							

S.E.M.—Standard error of the mean

St. D.—Standard deviation

B—Breast milk

P—Carbohydrate-modified cow's milk formula

Q—Same ingredients as P; flash sterilization

R—Evaporated milk, dextri-maltose formula

V—Simulated breast milk

W—Simulated breast milk, different brand

X—Formula with intermediate fat and protein content

For "t" values, see Table II

A baby's activity and sleeping time may affect water loss and hence fecal water. Variations due to temperature and humidity have been eliminated by maintaining them constant in our nurseries.

Alterations in the autoclave period, pressure or temperature may modify the formula and ultimately influence the stool.

Amniotic fluid and maternal blood aspiration affect gastrointestinal motility during the first few days of life, and retained meconium may modify the water content of transitional stools. Differences exist in milks obtained from different breeds of cows (7, 9) and from cows that are grazing or fed hay. Variations also exist in the composition of breast milk (7-14), especially in the first days. Our finding of a lower water percentage in stools of breast-fed infants is of interest particularly since these stools are usually reported of softer consistency than the stools of infants fed cow's milk (15). Colostrum is considered to have

a mild laxative effect (16), and it may be responsible for the increased water percentage of the breast-fed infant's stool in the first three and four days of life; the 5% glucose water supplements that breast-fed babies receive may also play a role (Fig. 1).

Stool water is influenced by the length of sojourn of the feces in the gastrointestinal tract. In adults, Steggerda has shown a decrease of from 6-23% in water content between the colonic and rectal ends of the stool (17, 18). Individual stool water content in the colonic end ranged from 70.18% to 85.58% and in the rectal end from 62.60% to 76.66%.

Holt and co-workers correlated stool water content with descriptive terms (19). The infants were on various diets and between four and thirteen months of age. Normal and diarrheal stool water percentages have been reviewed by Weil and Wallace (20). Normal stools were reported to have 80% (19), 82% (20) and 88% (21) with a range of 73% to 85% water according to Holt (19)

TABLE V
Fatty Acid Composition (Conc. 67 Calories/100 ml—20 Calories/oz)

	B	P	R	V	W	X
Fat w/v.....	3.8	2.8	2.66	3.4	3.7	3.0
Fatty Acids %						
Saturated	47	60	61	48	44	35
Unsaturated	53	40	39	52	56	65

B—Breast milk

P—Carbohydrate-modified cow's milk formula

R—Evaporated milk, dextri-maltose formula

V—Simulated breast milk

W—Simulated breast milk, different brand

X—Formula with intermediate fat and protein content

who classified 88% to 92% as "loose." "Very loose" or diarrheal stools contained 93% (19), 95% (21) and 97% (22) water.

We have shown that there is a marked variation in the percentage of water in the individual stool in the immediate neonatal period. It increased in the "transitional" period regardless of the baby's feeding regimen even if formula concentration was not increased rapidly.

Artificial preparations have come and gone since Powers' tabulation (23). Our results indicate no correlation between total protein, fat or carbohydrate in the feeding on the one hand and individual stool water percentage on the other. The mineral content, protein composition and the type of fat in the diet may be important. The feeding of milk containing a higher percentage of saturated fatty acids was associated with the higher stool water percentage (Tables IV and V).

The importance of the type of fat in the diet has been noted by Davidson (24) and Sweeney (25). Unsaturated fatty acids enhanced fat absorption whereas saturated fatty acids seemed to increase fat excretion.

We have some evidence that age up to ten weeks does not play an important

role in determining stool water content.* Babies were fed the milk preparations listed above. Their stool water content was found not to vary with age but according to the type of milk fed so that the range and average conformed to the values already reported (unpublished data). A decrease in stool frequency with advancing age of the baby has been reported (26).

SUMMARY

The water percentage of individual stools from newborn babies was analyzed. Babies were breast fed or fed various artificial milk preparations. They were studied in groups according to age, (3 and 4 day old babies and babies 5 days old and older), type of feeding, and formula concentration (45 calories per 100 ml and 67 calories per 100 ml).

Results show:

1. A wide range of stool water percentage at all ages on all feedings.
2. Significantly lower water percentage in meconium than in subsequent transitional stools studied up to the eighth day of life.
3. A statistically significant decrease in stool water percentage in breast-fed babies after the fourth day of life.
4. Formula concentration (within the limits of our study) did not seem to influence stool water percentage significantly.
5. After the fifth day significant differences were observed. Milks with higher percentages of saturated fatty acids were accompanied by higher individual stool water percentages; hence the type of fat in the formula may be important.

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The Buffering Capacity of Infants' Skins Against an Alkaline Soap and a Neutral Detergent

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There is relatively little in the literature on the pH studies of the skin surface in infants. No report has appeared on the buffering capacity of their skin against alkalis.

This study attempts to evaluate the buffering capacity of the skin of infants against an alkaline soap and a neutral detergent. Observations elicited from such a study may have physiologic and therapeutic implications.

MATERIALS AND METHODS

Twenty-five white infants ranging in age from two weeks to twenty-four months were studied. Ten babies were two to eight weeks of age and fifteen were two months to twenty-four months of age.

1. A neutral detergent bar consisting of an anionic detergent (acyl isethionate made by the condensation of sodium isethionate and fatty acids), a fatty emollient, a plasticizer, perfume and other minor ingredients.

2. Toilet Soap "A," a well-known soap bar consisting of a salt of a weakly ionized fatty acid and a strongly ionized alkali.

3. A Beckman Model-G pH meter was used. Fresh batteries were installed and a new combination flat bulb glass electrode, Beckman No. 39182, was used with thirty-six inch leads. This specific electrode was designed by Beckman Instruments for surface pH measurements such as skin pH. In order to measure pH accurately it is necessary to use a glass electrode constructed of pH sensitive glass rather than a metallic electrode.*

4. Continuously throughout this study before any measurements were made, the instrument and electrode were standardized with three known reference buffers. The three buffer solutions used had the following pH values: pH 4.0, pH 6.0, and pH 10.0. Three hundred milliliters of a 2% weight volume solution were prepared of the neutral detergent bar and of Toilet Soap "A." The pH values of the 2% solutions were as follows:

2% Detergent solution	pH 6.99†
2% Toilet soap solution	pH 10.20†
Distilled water used to make the solutions	pH 6.79†

5. In order to apply the 2% soap solutions and the distilled water to the infants' skins, Dupont cellulose sponges measuring two inches by two inches

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* Communication from Beckman Instrument Co.

† Corrected pH. Correction temperature:

18°C (291°K) = T_1 20°C (293°K) = T_2

$T = T_2 - T_1 = 20$ pH correction = 0.04

by one-half inch were used. The average dry weight of water or soap solution absorbed by each sponge was 34.7 grams.

6. Three different areas of the infants' skins were used. The volar surface of the right forearm was used for the application of the 2% soap solution. The volar surface of the right upper arm was used for the application of the distilled water. The volar surface of the left forearm was used for the application of the 2% detergent solution.

7. pH readings were made of the three areas of the infants' skins first using a few drops of distilled water. The values so obtained were reported as base levels for these three areas. The test solutions or distilled water were applied to their respective skin sites using individual cellulose sponges. The sponges were squeezed as completely as possible over the site to insure uniform application with all subjects. pH readings were made immediately after the application of the test solutions. The three skin sites were kept continuously moistened with their respective solutions for fifteen minutes.

8. Again pH readings were made of the three skin sites. The areas were dried with separate facial tissues and pH readings were again made of the sites. pH readings were now made of each area at the following time intervals:

- 15 minutes after drying skin site
- 30 minutes after drying skin site, and
- 60 minutes after drying skin site.

In total seven individual readings were made of each skin site:

1. Base level.
2. Wet initially with test solution or distilled water.
3. Wet for 15 minutes with the test solution or distilled water.
4. Dry (the skin sites were dried).
5. 15 minutes after drying skin site.
6. 30 minutes after drying skin site.
7. 60 minutes after drying skin site.

RESULTS

The pH of the skin on the volar right upper arm varied from 4.3 to 5.6. The pH on the volar surface of the left forearm varied from 4.1 to 5.9. The pH on the volar surface of the right forearm varied from 4.3 to 5.4. There seems to be no influence on the pH of the age and sex in the group studied here. The great majority showed a pH under 5.

Table I and Figure 1 summarize our study of the buffering capacity of the infants' skin. After application of the alkaline soap solution there was an average maximum rise of pH 8.77. In 25 trials or 78% of the total trials the skin sites to which the soap solution was applied required more than 60 minutes to return to their basic levels.

When the neutral detergent was applied there was a rise in pH to 6.67 in 15 minutes. In comparison to the action of the alkaline soap solution only 6%

of the trials or 2 of the skin sites to which the detergent solution was applied required more than 60 minutes to return to their base level (Table I). Or it may be said that in 29 trials or 91%, the skin sites to which the neutral detergent solution was applied returned to their base levels within 60 minutes or less;

TABLE I
*pH Values Obtained on Infants' Skins Before, During, and After Application of Test Solutions**
(32 Trials on 25 Infants)

	Base Level	Wet Initially	Wet 15 min.	Dry	Dry 15 min.	Dry 30 min.	Dry 60 min.
<i>Toilet Soap "A"</i> (volar surface of right forearm)	4.77	8.82	8.77	7.32	6.38	5.81	5.27
<i>Neutral Detergent Bar</i> (volar surface of left forearm)	4.78	6.71	6.67	5.75	5.24	4.95	4.73
<i>Distilled Water</i> (volar surface of right upper arm)	4.69	4.71	4.70	4.70	4.71	4.70	4.69

* pH values are average readings.

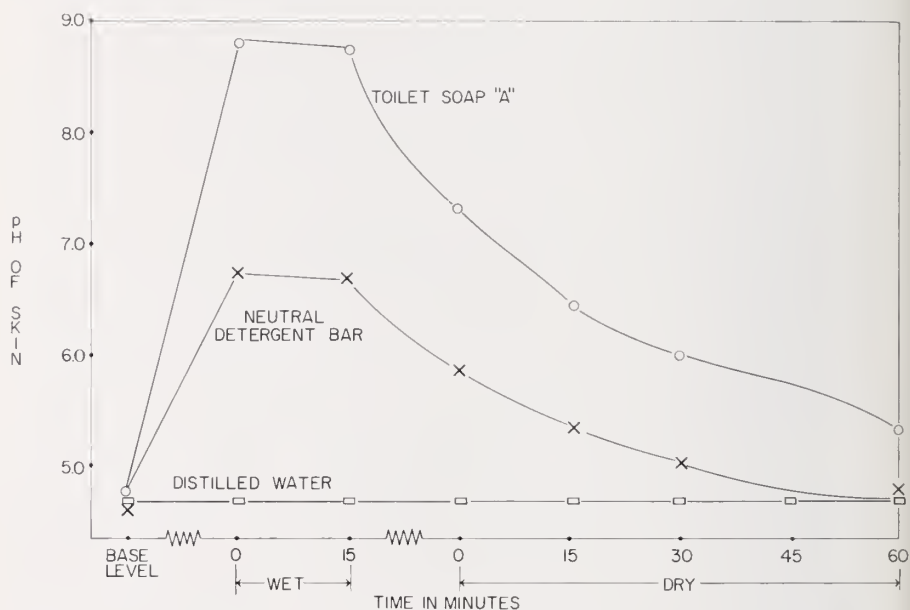


FIG. 1. Length of time required for pH of infants' skins to return to base level after application of various soap solutions and distilled water.

whereas the skin sites to which the soap solution was applied, only 7 or 22% returned to their base levels within 60 minutes or less.

Since no apparent differences on the pH values could be noted in babies in the two to eight week group and the babies in the two months to twenty-four months group, the data was combined and summarized in Table I and Figure 1.

COMMENT

Bear, Cheeseman *et al.* (1) have confirmed the observations of Behrendt and Greene (2) that the pH of the skin surface of the newborn was more alkaline approximately 6.77 on the first day, 6.27 on the second day, 6.03 on the third day, 6.12 on the fourth day, 5.86 on the fifth day, 5.93 on the sixth day, 6.01 on the seventh day and 6.06 on the eighth day. They indicated that the pH of the skin surface is likely to be highest on the first day then falls to a minimum about the fifth day and then rises slightly thereafter.

Behrendt and Greene (2) concluded that during the first two days of life about 50% of the infants have abnormally alkaline reactions although this decreases so that by the end of the first week most have a normal acid skin pH.

We noted no difference in the pH values of the skin in the areas which we studied, between the babies from two weeks to twenty-four months of age. Apparently in our age group the pH of the skin surface was comparable to that of the adult. There seems to be a greater strain on the buffering capacity of the skin when the soap solution of about pH 10 is used than when a neutral detergent of about pH 7 is used. Frequent use of soap in washing especially when the buffering capacity is reduced may explain intolerance of infants to soap.

SUMMARY

The pH on the skin on the arms of infants two weeks to twenty-four months of age is approximately the same. The great majority showed a pH under 5 and ranged from a pH of 4.1 to 5.9. There seemed to be no influence of the age and sex on the pH of the group studied.

Immediately after washing with a soap solution of about pH 10, the pH of the dried skin rose an average of 2.55 units in contrast to a pH rise of only 0.97 units right after the use of a neutral detergent.

In 75% of the total trials the skin sites to which the soap solution was applied required more than 60 minutes to return to their respective base levels. When the neutral detergent solution was applied only 6 of the skin sites failed to return to their base levels in 60 minutes or less.

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CLINICO-PATHOLOGICAL CONFERENCE

Dyspnea, Cyanosis and Chest Pain in a Young Woman

Edited by

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A 31 year old white housewife was admitted to The Mount Sinai Hospital for the seventh time because of severe dyspnea for four years.

She was well until the age of 27 years when, after the birth of her baby, she noted the onset of dyspnea and pressure in the left chest and arm following exertion. She also developed a nonproductive cough and required several pillows to sleep at night. X-rays revealed haziness in both lung fields and an electrocardiogram showed right ventricular hypertrophy and right axis deviation. The patient was started on steroids with slight improvement in exercise tolerance but with a 25 pound weight gain, rounding of the face and abdominal striae. After several months, the medication was discontinued and, within two weeks, dyspnea and chest pain recurred. The patient had no fever or pleuritic pain and no pertinent past or family history. She had one child who was well.

Cushingoid features were apparent on examination. Pulse was 112/min. and regular; respirations 14/min.; and blood pressure 130/100. The heart was enlarged. A presystolic gallop was best heard along the left sternal border. P_2 was greater than A_2 . No murmurs were heard. The lungs were clear. The liver was tender and its edge was felt two fingerbreadths below the right costal margin. Slight pitting edema of the ankles was noted. No cyanosis or clubbing was seen.

Pertinent laboratory tests are in Table I. Electrolytes, calcium, phosphorus, urea and sugar were all normal and remained so throughout the subsequent hospital admission. The results of liver function tests were normal. Many lupus preparations, Kveim test, latex fixation, cryoglobulin test, tuberculin and histoplasmin skin tests, and the serology were negative. No significant number of red blood cells and no abnormality of the white blood count or bone marrow except for a left shift were noted. Serum electrophoresis was normal, as was urinary 5HIAA excretion.

Chest x-ray showed interstitial infiltration of both lung fields, more pronounced in the bases. The diaphragms were not depressed. The heart size was at the upper limit of normal. The pulmonary artery segment was prominent. No emphysematous blebs or hilar adenopathy were seen. The dorsal spine was normal. An electrocardiogram showed a regular rate of 110/min., peaked P in 2, 3 and aVF, RSR' in V_1 , tall R and deep S in V_{2-6} , and T inverted or diphasic in V_{1-4} . Pulmonary function tests showed evidence of an alveolar-capillary block.

The patient improved on bed rest and left the hospital after five days. She was placed on digoxin and chlorothiazide. Her symptoms did not progress for

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two years, at the end of which time she was readmitted for evaluation. Amenorrhea had been present for about seven months. The patient was tachypneic with respirations of 27 min. The blood pressure was 110/70. No cyanosis nor clubbing was present. Some hepatojugular reflex was elicited. Bibasilar rales were heard in the chest which increased on deep inspiration. P₂ was much louder than A₂ and split. A loud systolic murmur was heard along the left sternal border. The rest of the examination was the same as two years earlier. Gynecological examination disclosed no abnormalities.

Venous pressure was 170 mm with a rise to 200 mm on pressure over the liver. Decholin circulation time was 18 sec. Pertinent laboratory data are in Table I.

TABLE I
Pertinent Laboratory Data

	1st Admission	2nd Admission	3rd Admission		4th Admission	5th Admission	6th Admission	7th Admission
			Pre-operative	Post-operative				
		(after 2 yrs)	(after 6 mos)		(after 6 mos)	(after 4 mos)	(after 1 mo)	(after 1 mo)
Hematoerit (%)	—	52	52	31.5	57	—	52	59
Hemoglobin (Gm%)	15.2	15.6	16.7	10	16.2	16.2	14.4	15.9
WBC/mm ³	9,900	13,500	13,000	19,000	12,750	8,250	13,000	13,000
ESR (mm/hr)	22	7	10	22	30	—	20	—
CO ₂ (mEq/L)	22.5	24.2	28.2	24	23.2	23.7	34.6	17.8
Albumin (Gm%)	4.0	3.9	4.1	—	4.0	—	4.0	—
Globulin (Gm%)	3.0	3.5	3.9	—	3.3	—	2.5	—
Alkaline Phosphatase (KAU)	7.6	—	10.3	19.4	22.4	—	—	—
Uric Acid (mg%)	—	—	—	—	6.4-11	—	9.8	—
Albuminuria	tr	0	+	tr	2+	tr	2+	tr
Urine WBC	8-10	0-2	0-2	2-3	6-8	occ	2-4	0-1

Chest x-ray was unchanged except that the heart was somewhat larger and the pulmonary segment more prominent. Electrocardiogram was unchanged. After the studies were completed, the patient was sent home. She was well for six months after which she suddenly began gaining weight and severe dyspnea recurred. Mercuhydrin gave some relief. A week later she developed right upper quadrant pain and anorexia requiring narcotics. This pain was colicky and radiated to the back. Because this did not go away, the patient was admitted for the third time. The amenorrhea continued. On examination slight cyanosis was seen but the patient could lie comfortably in bed. No clubbing was present. The systolic murmur was judged to be louder and increased with respiration. It was heard all over the precordium and did not radiate to the axilla. The lungs were clear. The liver was enlarged and tender as before with more tenderness in the gallbladder area.

The pertinent laboratory data are in Table I. Chest x-ray was unchanged.

Gallbladder x-rays showed faint visualization and many small somewhat calcified stones. No significant change was seen in the electrocardiogram. Venous pressure was 175 mm with an increase to 215 mm on hepatic pressure, and circulation time was 22 sec. Because of persistence of right upper quadrant colic and a slightly increased serum bilirubin, a cholecystectomy was performed and a thickened gallbladder containing stones was removed. Postoperatively she did well except that serum bilirubin rose gradually to 5.1 mg% with about half conjugated. Leukoeytosis and increased serum activity of alkaline phosphatase occurred simultaneously. On the fifth postoperative day, she experienced some right upper quadrant pain, nausea, and temperature elevation. This persisted for two days, subsided, and recurred on the tenth postoperative day. Hemoglobin dropped sharply although the Coombs test was negative. This improved slowly as the symptoms subsided and the patient returned home on the sixteenth postoperative day on Chloromycetin. She also took chloroquine, digoxin and Hydrodiuril.

While home she developed symptoms of gout and was also given colchicine. The patient noted recurrent fever and pleuritic chest pain particularly on the left side with some radiation to the left arm. Because of several severe attacks of these, she was readmitted six months after her last discharge. Vital signs were as on previous admissions. Cyanosis was seen but no clubbing. Basilar rates and rhonchi were heard. In addition to the harsh systolic murmur previously noted, a thrill was felt. The liver was slightly enlarged and tender. The remainder of the physical findings was unchanged. The patient was placed on anticoagulant therapy and despite mild brief hypotensive episodes with chest pain, she gradually improved and went home after ten days.

At home she developed episodes of severe dyspnea and right upper quadrant pain requiring frequent injections of narcotics and not relieved by oxygen inhalations. After four months she was admitted to the hospital for the fifth time because the symptoms were getting worse. Cyanosis was present. The lungs were clear. Blood pressure was 100/70 and the heart rate was 120/min. The harsh systolic murmur, now described as crescendo in type, was loudest over the xiphoid and transmitted to the axilla. The rest of the physical findings were unchanged. Laboratory data are in Table I. Chest x-ray indicated increase in the pulmonary infiltration and further enlargement of the pulmonary arteries. An abdominal film showed calcifications in the iliac arteries but no other abnormalities. Electrocardiogram did not change significantly. The patient improved on sedation and she was discharged in five days still taking anticoagulants, digoxin and Diamox, in addition.

The patient developed weakness, palpitations, and increasing dyspnea necessitating rehospitalization within a month. No significantly different physical or laboratory findings were obtained. The patient was started on prednisone 40 mg a day and this was reduced to 20 mg a day before the patient was discharged on the sixth day. Despite all the auscultatory findings, phonocardiography revealed only a short late diastolic low intensity murmur of uncertain significance in the pulmonic area.

While home the patient began to be confused, lethargic, and increasingly dyspneic. She was readmitted for the seventh and last time after a month. Blood pressure was 92/70, respirations 36/min., pulse 96/min. and temperature normal. She was cyanotic but had no clubbing. The neck veins were distended. The expiratory excursions of the chest were shallow. Bilateral crepitant rales were heard. The heart was not greatly enlarged. A loud systolic murmur was heard loudest over the lower sternum. It seemed to carry over into diastole. Striae were on the abdomen. The liver edge was down 4 to 5 fingerbreaths. The organ was tender and hepatojugular reflux was noted. Pedal edema was present. The morning after admission the patient developed vasomotor collapse which did not respond to Levophed, intravenous steroids, or a Bird respirator. She died after one day in the hospital and four years after the onset of symptoms.

*Dr. Mortimer E. Bader**: The patient had arterial blood studies which are not in the protocol. The findings in the patient when first seen were oxygen content 16.3 vol%, capacity 21.0, which was slightly elevated, and arterial oxygen saturation 79%. CO₂ values were low, due to the fact that she was hyperventilating. These findings are rather characteristic for either an alveolar-capillary block syndrome or a pulmonary A-V shunt. The fact that she was hyperventilating is more in favor of the former. The studies of the diffusing capacity are most compatible with an alveolar-capillary block syndrome in that there is well-preserved maximum breathing capacity without any evidence of CO₂ retention—indeed, a lower value than normal for CO₂ was present.

Since this illness followed immediately or shortly after a pregnancy, the possibility of recurrent pulmonary embolism has to be considered as well as the alveolar-capillary block syndrome. The alveolar-capillary block syndrome is characterized clinically by bibasilar rales in the chest, tachypnea, and hyperpnea, roentgenologically by a small chest volume, and physiologically by the findings of a well-preserved residual volume/total capacity ratio, an increase in the work of breathing, reduction in diffusion capacity of the lungs, a decrease in pulmonary compliance, and a perfectly well-maintained airway with resistance in the normal range.

This physiological definition of this syndrome offers a springboard for differential diagnosis in this case because many diseases are included in this physiological syndrome. Actually, an even larger variety have been described causing interstitial infiltrations but not all of these have had physiological studies and perhaps some of them would also demonstrate an alveolar-capillary block syndrome.

For the sake of completeness, but not because I consider them seriously, one should mention gas poisoning such as phosgene, sulfur dioxide, silo-filler's disease due to oxides of nitrogen and moldy forage, and farmer's lung. None of these needs to be considered seriously.

Pneumoconioses due to mineral agents such as beryllium, asbestos or possibly tale, do not play a significant role.

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We might look at the x-rays at this time.

*Dr. Mansho T. Khilnani**: Over a period of three years, very little change was noted except that the size of the heart increased. The chart uses the term "interstitial process" to describe the lung fields and it is an interstitial process but it was forming a sort of a cystic or so-called honeycomb lung. It did not have the patchy infiltrations that accompany silicosis or silico-tuberculosis or even nodular infiltrations of miliary tuberculosis. The heart had a rounded body contour which was primarily right ventricular enlargement. The volume of the lung was not increased. The diaphragms were not depressed. There were no large blebs.

This process could have developed on the basis of various types of granuloma or some form of interstitial fibrosis or interstitial myomatosis. From the x-ray point of view, it is hard to tell with certainty. The only thing we can say is that this is a honeycomb lung. The x-rays also showed biliary calculi which did not appear to be pigmented stones. There was nothing in the spine, and the kidneys were normal. The liver was of normal size.

Dr. Bader: Having eliminated gases and pneumoconioses, we have to consider the possibility of certain infectious processes which could be responsible. These would include miliary tuberculosis, which we have just heard Dr. Khilnani say is not very likely from this appearance, but one cannot always exclude it on x-ray grounds. The absence of the febrile course and the presence of the negative tuberculin test tend to rule that out.

Miliary carcinomatosis is a possibility, but the duration of the disease is strongly against that explanation. In connection with malignancies, I might mention that occasionally this type of syndrome may be seen with pulmonary adenomatosis, but the sputum production in those cases is enormous, and it is not so described here.

Radiation fibrosis can produce an interstitial disease process with alveolar-capillary block, but there was no radiation in this case.

This brings us to that large group of cases of unknown origin which include sarcoid granulomas. Sarcoidosis would have to be considered in any case of interstitial disease. We have no evidence of hyperglobulinemia, and calcium was normal. Also a Kveim test was normal so that if this is sarcoidosis, I do not know how the diagnosis could be made in the absence of a biopsy of the lung with these other findings being normal.

In differential diagnosis in this type of process, I might stress that a scalene biopsy and a lung biopsy are almost mandatory in many instances unless collateral clinical evidence gives some clue to the etiology.

We would have to consider the possibility of progressive pulmonary scleroderma. Pulmonary involvement with scleroderma in the absence of the conventional changes of the skin has been reported, but it certainly is an infrequent event to find isolated pulmonary involvement. In most of these cases reported where it was present prior to the appearance of skin lesions, skin lesions did

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become manifest before the patient died, so it is safe to say that, in the absence of associated skin lesions, if scleroderma is present, it would be a novel case.

Among the other so-called collagen disorders, periarteritis nodosa does not usually produce a lesion like this. It is associated with eosinophilia, hyperglobulinemia, and leukocytosis, none of which is present in this case, so that I think we can dismiss it.

Cardiac disease per se may produce an interstitial fibrosis in the case of mitral stenosis where secondary hemosiderosis may occur, and has to be considered. This looked like a mitral heart but she did not have a diastolic murmur of significance. She is described as having a faint diastolic murmur in the pulmonic area, which would have represented some functional pulmonary change. If this is secondary pulmonary hemosiderosis, it is unusual.

Similarly, atrial-septal defects have been known to produce alveolar-capillary block, but she had no history of any murmur. She was not sick prior to her pregnancy, and while it is possible that a murmur was previously present but picked up for the first time subsequent to the progressive difficulties, the situation here would suggest that her cardiac enlargement was secondary to the pulmonary process, and not vice versa.

This raises the question whether she had primary pulmonary hemosiderosis. This does occur in adults although it is much more common in children. One out of five cases occurs in adults up to the mid-forties. Pulmonary hemorrhage is always present so that we can easily exclude that diagnosis.

Now we come to some of the rare causes. Histiocytosis-x has been reported to produce a typical alveolar-capillary block but it was manifested in association with characteristic lesions of the skull and other organs. It is often associated with diabetes insipidus, which may be seen with Hand-Schüller-Christian disease. Unfortunately, we do not have a skull film here. If there is no evidence elsewhere pathologically of Hand-Schüller-Christian disease, this diagnosing is difficult because there is nothing etiologically significant in the interstitial fibrotic process in the lung. Even if a lung biopsy had been done, the diagnosis could not be proved. Eosinophilic pneumonia is ruled out by the absence of eosinophilia. Eosinophilic granuloma, which is believed by many to be a variant of the Hand-Schüller-Christian syndrome, has been reported to cause this syndrome but I have no evidence for that diagnosis in this patient.

That leaves two main classes of disease, so-called Hamman-Rich syndrome (interstitial fibrosis) and/or granulomatosis of unknown etiology, and, also, recurrent pulmonary embolism. There may be several diseases included in interstitial fibrosis without apparent etiology.

The newer ones which are included as causes of interstitial disease are rheumatoid lung, except our patient had no arthritis, or lupus erythematosus, but this is unlikely by virtue of the absence of collateral clinical manifestations. Primary pulmonary hypertension can be dismissed because lung function is always normal and the lung picture is essentially normal. Primary vascular endosclerosis brings us back to the age of Ayerza* and is best forgotten.

* Abel Ayerza, Argentine physician, 1861-1918.

We are left with interstitial fibrosis of unknown origin, which could nicely be classified as Hamman-Rich disease. The microcystic changes, however, are compatible with the changes described in histiocytosis-x, scleroderma, and a few other conditions.

One diagnosis that I did not mention is microalveolar lithiasis which can be caused by x-rays, but we will forget this.

What about recurrent pulmonary embolism? The disease started immediately after the pregnancy. By virtue of destruction of the vascular bed and reduction of the diffusing surface of the lung, a reduced diffusing capacity results. Cases of pulmonary embolism are reported which are indistinguishable from alveolar-capillary block, and, indeed, the issue is always raised whether the atherosclerotic changes reflect primary pulmonary hypertension in which thrombosis took place, or whether thrombosis took place in the lung with subsequent recanalization.

I was curious whether amniotic fluid embolism could cause chronic disease, not in the sense that it could keep recurring, but whether it could imitate a fibrotic reaction. While it is usually fatal, several cases are believed to have survived. Such a case is described in which a syndrome started not immediately after pregnancy but within a few months and progressed to full-blown interstitial disease of the lung.

I prefer to think that this type of picture is not what one would see with recurrent pulmonary embolism, and I am left with a diagnosis of interstitial fibrosis of unknown origin, or Hamman-Rich syndrome. I think review of the causes of alveolar-capillary block syndrome, as has been discussed here, leaves one without collateral clinical evidence for another diagnosis. If this patient should have some specific etiological diagnosis, such as scleroderma of the lung or sarcoidosis, I do not believe that the diagnosis can be made on clinical grounds. If it should prove to be a new entity, causing an alveolar-capillary block syndrome, then I will have learned something.

*Dr. Emanuel Rubin**: Thank you very much, Dr. Bader, for an illuminating and certainly complete discussion of the problems which puzzled the clinicians.

Dr. Louis E. Siltzbach†: I saw this patient twice, and I would like to add one or two comments about the case. I saw her initially at the onset of her illness. A lung biopsy was recommended because we thought she had Hamman-Rich disease even though she did not have two of the findings which occur in about 75 per cent of cases of long standing, namely, clubbing of the fingers and hypergammaglobulinemia. It seemed quite apparent that we were dealing with an interstitial lung process but since we lacked the other diagnostic leads to other conditions that Dr. Bader mentioned, we assumed that this woman had a so-called Hamman-Rich syndrome. We watched her develop increasing right heart failure. She never showed any evidence of pulmonary embolization or of pulmonary infarction. We also felt that the reticulation and the microcysts in the lungs were quite compatible with an advancing idiopathic diffuse pulmonary

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fibrosis of the Hamman-Rich type. We considered the microcysts as probably more characteristic of a Hamman-Rich syndrome than of almost any other interstitial lung disease in terms of relative and absolute frequency.

The second time that I saw her some three years later there was a question of whether she could be operated upon for gallstones. She was having such severe attacks of right upper quadrant pain an empyema of the gallbladder was considered. At this time we felt she was doing so well as far as her lungs were concerned, that operation could be risked. Patients with interstitial lung processes endure anesthesia much better than do patients with obstructive lung disease.

I would like to call to your attention the fact that the domes of the diaphragm

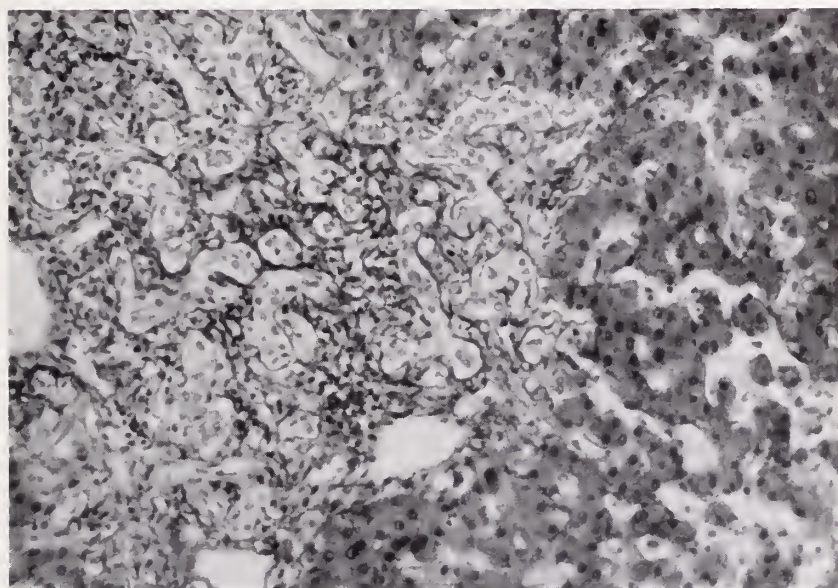


FIG. 1. Section of liver showing enlarged portal tract and ductular proliferation. Trichrome ($\times 150$).

never came up very much, which is unusual in Hamman-Rich syndrome, but we have seen normally placed diaphragms occasionally in patients with idiopathic interstitial fibrosis who survive as long as this. Those whose diaphragms ascend rapidly die sooner.

Dr. Bader: That is the only diagnosis that seems reasonable, in the absence of any other findings, but it will probably turn out to be wrong.

Dr. Rubin: At autopsy, passive congestion affecting many organs was very prominent. The liver showed a conspicuous reticulated pattern characteristic of passive congestion. In the centrolobular zones of the liver, necrotic cells were replaced by red cells showing that this was a process of long standing. The portal tracts showed fibrosis which we also associated with chronic passive congestion of the liver of long standing (Fig. 1).

The spleen was moderately enlarged and severely congested.

The kidneys were slightly enlarged. The glomeruli were slightly enlarged, a finding associated with cyanosis of long standing.

The pancreas showed circular fibrosis in a daisy arrangement which is characteristic of severe passive congestion.

In the heart, the left ventricle was normal and there was no evidence of any valvular disease. However, as was expected from the clinical data, the right



FIG. 2. Cross sections of right ventricle (right) and left ventricle (left) showing severe right ventricular hypertrophy.

heart was markedly hypertrophied. The thickness of the right ventricle was about three times the normal, characteristic of extreme cor pulmonale (Fig. 2), with hypertrophied myocardial fibers. She had a moderate myocarditis, the etiology of which is not entirely clear. Patchy interstitial fibrosis of the right ventricle was found. Whether this resulted from a hypertrophy of the right ventricle outgrowing the blood supply or from a chronic myocarditis, I am not prepared to say. However, it did not affect her in a significant manner, because the pathology was certainly isolated and patchy.

We saw on the surface of the lung numerous small vesicles. These small cystic areas were diffusely scattered over the surface of both lungs without any predilection for either lung nor any focal area.

We knew as soon as we saw these lungs and from the clinical history that the pathology would be quite interesting, and in order to preserve the structure of the lungs, we inflated the lungs with formalin before opening them, after which we bisected the lungs. As we suspected from the appearance of the pleural surface, the entire lung was involved with small cysts, with no part of the lung spared (Figs. 3 and 4). The numerous small cysts were of varying



FIG. 3. Right lung bisected after inflation with formalin. Note diffuse cystic change.

sizes, some reaching 2 centimeters in diameter, but most were only a few millimeters in diameter. This was a diffuse, generalized, cystic disease of the lung, which was generally microcystic, but showed larger cysts as well.

As we suspected, the main pulmonary artery showed severe atherosclerotic change, which was compatible with and practically diagnostic of severe pulmonary hypertension.

The walls of most of the cysts were quite thin with the exception of a few focal areas of thickening, usually near bronchi.

Some cystic areas were lined by bronchial epithelium and some were not. At one time perhaps all had bronchial epithelium, but the appearance was no longer uniform. This was not metaplasia of alveolar epithelium, such as is de-

scribed in Hamman-Rich and in scleroderma, but was actually normal bronchiolar epithelium. Since we saw no cartilage accompanying the cysts, we could not call the epithelium bronchial.

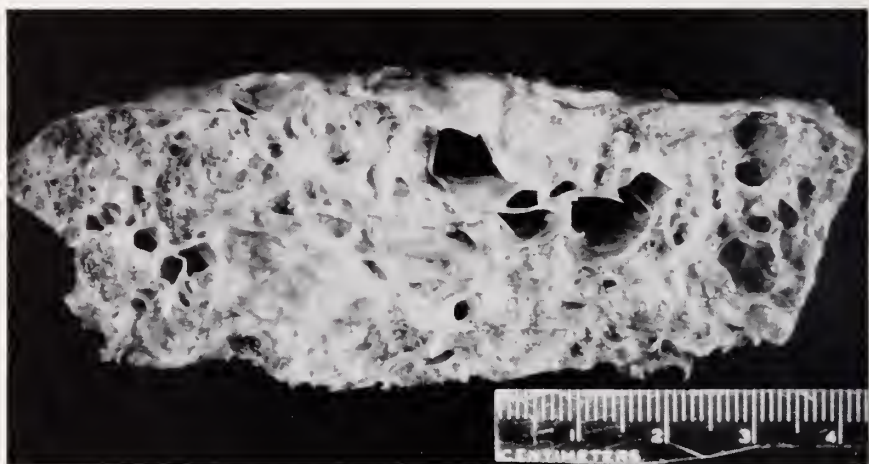


FIG. 4. Higher power of portion of right lung.

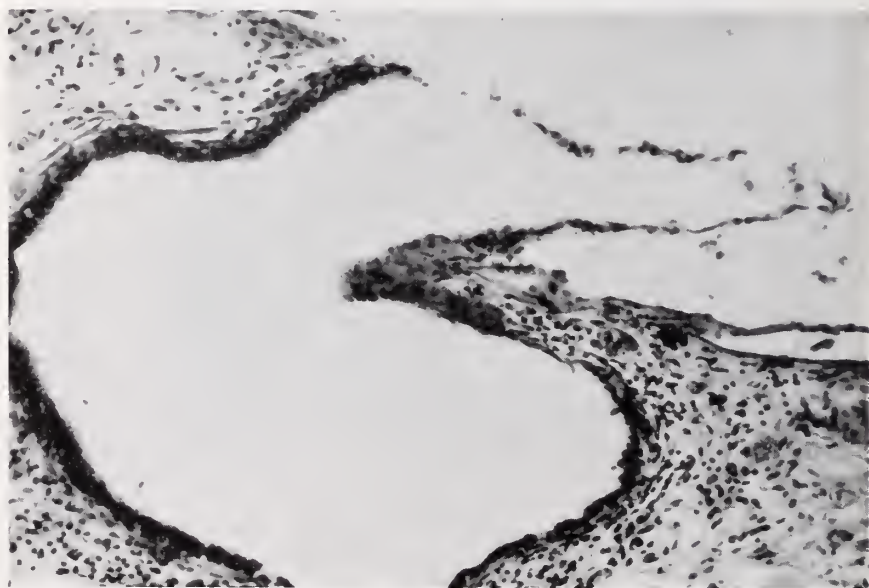


FIG. 5. Dilated bronchiole entering cyst. H & E ($\times 150$).

Many of these dilated cystic bronchioles could be seen to open into large cystic areas (Fig. 5) which also showed remnants of the cuboidal bronchiolar epithelium with no evidence of severe fibrosis.

The parts of the lung which apparently permitted her to have respiratory

exchange were severely emphysematous on a compensatory basis, and, in these areas, the alveolar walls were quite thin. The normal alveolar structure in these areas is what kept her alive. Certainly these areas were not cystic, although all were emphysematous. She did apparently have some chronic lung infection, because inflammatory foci were found around a few small bronchioles (Fig. 6).

The bronchiolar epithelium was not entirely normal in several areas, displaying a papillary appearance and occasionally polyp formation.

Small pulmonary arteries were thickened, as evidence of pulmonary hypertension. There were many areas where the pulmonary capillaries were widely dilated and severely congested, giving, in some areas, an almost angiomatoid

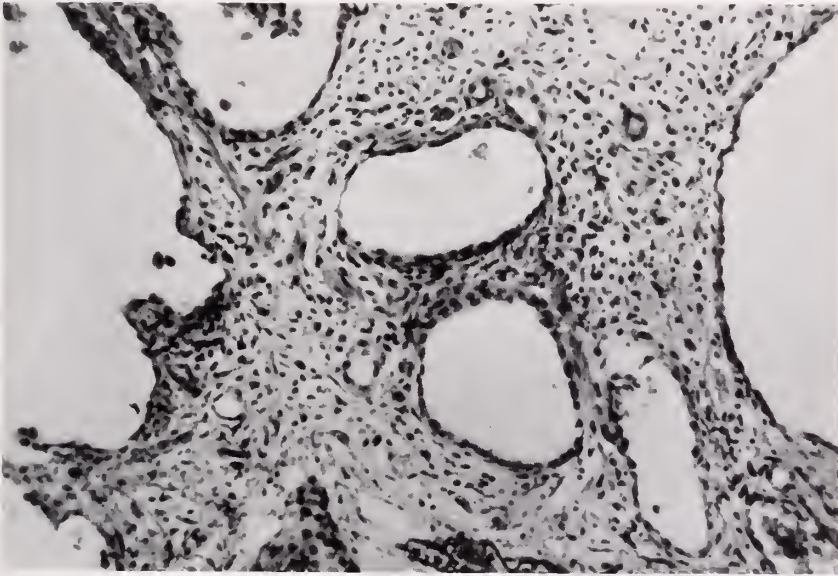


FIG. 6. Dilated bronchioles surrounded by chronic inflammation. Larger cysts retain bronchiolar epithelium. H & E ($\times 150$).

appearance. Whether this was on a congenital basis or represented compensatory intrapulmonary shunts, I cannot say. Certainly it was a prominent feature in the lung.

Now we are faced again with the problem of diagnosis. It was difficult and puzzling clinically, and it puzzles us also. The descriptive diagnosis of honeycomb lung is entirely correct, but it differs from the usual microcystic disease in having few larger cysts.

Here are some of the causes of honeycomb lung (Table II). This is by no means an entirely complete list, but it will give you an idea of the type of things that you have to think of when you see a honeycomb lung on x-ray. Foreign body granulomas, asbestosis, and berylliosis can cause honeycomb lung by granuloma formation and fibrosis, but she had neither the occupational history nor the histologic evidence.

The xanthomatoses certainly could cause it, but there is no evidence anywhere of these diseases.

Some people, especially the English, consider fibroleiomyomatosis, which is called by others muscular cirrhosis of the lung, bronchiolar emphysema or bronchiolectasis, to be a hamartoma, while others have concluded that this is really a hyperplasia of smooth muscle, as a reaction to any type of chronic pulmonary disease.

At any rate, this is excluded because smooth muscle was conspicuously absent in this lung.

Tuberous sclerosis is a hamartomatous disease, but is also excluded on histologic grounds.

We come now to sarcoidosis. Two years ago we had a Clinico-Pathological Conference in which the diagnosis was sarcoidosis with a honeycomb lung.

TABLE II

Causes of Honeycomb Lung

1. Foreign body granulomas
 - asbestosis
 - berylliosis
2. Xanthomatoses
 - eosinophilic granuloma
 - Hand-Schüller-Christian
 - Letterer-Siwe
3. Hamartomas
 - fibroleiomyomatosis
 - tuberous sclerosis
4. Sarcoidosis
5. Post-influenza?
6. Scleroderma
7. Hamman-Rich (occasionally with rheumatoid arthritis)
8. Congenital

Again we must rule this out because we found no granulomas.

The observed pathology might be considered as post-influenzal. Many observers have suggested that a chronic interstitial pneumonia may weaken the lungs, so that subsequent fibrosis may lead to honeycomb lung.

Scleroderma or systemic sclerosis is certainly a possibility, as Dr. Bader mentioned, and the radiologic appearance of the lung is entirely consistent with that. However, nowhere did we find evidence of scleroderma, and I think we definitely have to rule that out.

The Hamman-Rich syndrome, or acute interstitial fibrosis of the lung, occasionally seen with rheumatoid arthritis, was considered. Certainly she did not have rheumatoid arthritis. However, this might have been a pure Hamman-Rich syndrome because interstitial fibrosis of the lung is known to given microcystic disease and is the most common cause in this country of the honeycomb lung. We were unable to document this in any section of the lung that we took. Nowhere did we see any chronic inflammation in the alveolar septa nor any

good focus of interstitial fibrosis, I do not believe that the diagnosis of Hamman-Rich is tenable here, in the absence of any histologic evidence.

We come now to the last possibility. There are several reasons for believing that this woman had a congenital disease. One is its thoroughly diffuse nature. While the Hamman-Rich syndrome and scleroderma frequently do produce a honeycomb lung, it is usually more prominent in the outer or lower portions of the lung. Here we found no predilection for any part of the lung. Another reason is the variation in size of the cysts, some reaching 2 cm in diameter.

The absence of any of these other etiologies and the presence of the large bronchiolar element leads us to believe, although we cannot absolutely prove, that this case represents a dysplasia or malformation of the bronchiolar and alveolar elements of the lung.

Cases of primary or congenital alveolar dysplasia were described in infants who died shortly after birth (1). In those infants who presumably died of fetal atelectasis, there was a relative diminution in the size of the pulmonary alveoli in relation to the size of the bronchioles, and many of the bronchioles were actually dilated and almost cystic. Although those children died, it is certainly conceivable that some could live with a milder degree of alveolar dysplasia. With increasing stress of respiration during life, these small, dilated, weakened bronchioles might expand, with all the other secondary consequences.

Our opinion is that this woman had a variant of either a primary bronchiolar or alveolar dysplasia which was mild enough to allow her to live for 31 years, but because of the secondary effect of infection and the stress of respiration, it eventually developed into a cystic disease with accompanying pulmonary hypertension.

Dr. Bader: In reviewing all the causes for this syndrome, I have never seen congenital microcystic disease of the lung listed, and I will now have to think of it in such a differential diagnosis.

Dr. Clifford Spingarn:* Were any studies made of the genital system?

Dr. Rubin: Many sections of the genital organs were studied but they showed very little. The ovaries showed many follicles which had recently ruptured despite the history of amenorrhea.

Dr. Spingarn: One of the puzzling features of the case was that following her pregnancy and after she started on steroids, she never regained menstrual function.

Dr. Rubin: I am unable to explain the amenorrhea, since there were no gross or microscopic abnormalities in the ovaries.

Dr. Siltzbach: I found this case extraordinary in several respects, but if you are willing to remove sarcoidosis as one of the causes of fibrocystic lung, I would be happier. In the case that you referred to, there was severe bullous emphysema which is quite different from the microcysts we are talking about here.

Dr. Rubin: Dr. Siltzbach is correct. Those cysts were considerably larger.

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Dr. Stiltzbach: It is rather remarkable that a woman would live for 31 years with these lungs. Are you assuming that these lesions remained exactly the same for her entire life?

Dr. Rubin: I assume that she started out with a relatively mild congenital dysplasia, either of the alveolar structures or of the bronchiolar structures, and that this gradually progressed during her lifetime, with infection making it worse.

Dr. Stiltzbach: May I interrupt you? She never gave much evidence of added infection. One of the things that was quite characteristic of this woman was that she never developed ventilation difficulty. She never had very much expectoration. She was free, as are many of the cases of Hamman-Rich syndrome, of pulmonary infection until the very end.

Dr. Rubin: She certainly had peribronchiolar inflammation, but it is my feeling that she did not get into any difficulty until pulmonary hypertension or the encroachment upon her reserve was so great that it became symptomatic.

Physician: Was there a chest x-ray obtained prenatally?

Dr. Spingarn: Apparently there were none, but she was delivered elsewhere, and perusal of the records indicated that there was nothing to indicate that there was any cardiopulmonary difficulty. She, herself, had a perfectly normal delivery and was followed carefully by her physician through her childhood and adolescence, and there was nothing to indicate any previous pulmonary difficulties.

I would like to ask Dr. Stiltzbach a question. For about a year and a half, she was on empirical chloroquine treatment because of her inability to respond to steroids. Do you think this drug could have modified the effect of the inflammatory reaction?

Dr. Stiltzbach: I do not know of a case quite like this so I am unable to pinpoint on any single factor to explain the clinical course and pathologic findings. We have treated a good number of patients with sarcoidosis with chloroquine now, and we have noted regression of granulomatous lesions with this drug. I have treated a few cases of idiopathic diffuse interstitial pulmonary fibrosis with chloroquine without notable improvement.

Final diagnosis: 1. CONGENITAL CYSTIC DISEASE OF THE LUNG (PRIMARY ALVEOLAR DYSPLASIA?) 2. COR PULMONALE.

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RADIOLOGICAL NOTES

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CASE NO. 228

An 18 year old boy consulted his physician for removal of a small mass in the right parietal region. The mass was first discovered at least six years previously; it was nontender and there were no associated symptoms. However, a recent increase in size was noted associated with pain and tenderness. On examination, the swelling was considered to be a sebaceous cyst or lipoma and a local excision was attempted. This was discontinued when the lesion was found to be located deep to the temporal fascia. Radiographic examination of the skull then revealed a smoothly outlined erosive lesion of the right parietal bone with central lucency and marginal sclerosis (Fig. 1).

The radiographic impression was that of a dermoid cyst. Physical examination was otherwise negative. Electroencephalogram and right carotid angiogram were normal.

At surgery, the tumor had extended through a small area in the outer table. The inner table was intact throughout. The mass was completely encapsulated but firmly adherent to the underlying bone; it was completely excised. It proved to be a cyst containing sebaceous material and hair and histological examination confirmed the diagnosis of dermoid cyst.

Case Report: DERMOID CYST—INTRADIPOIC TYPE.

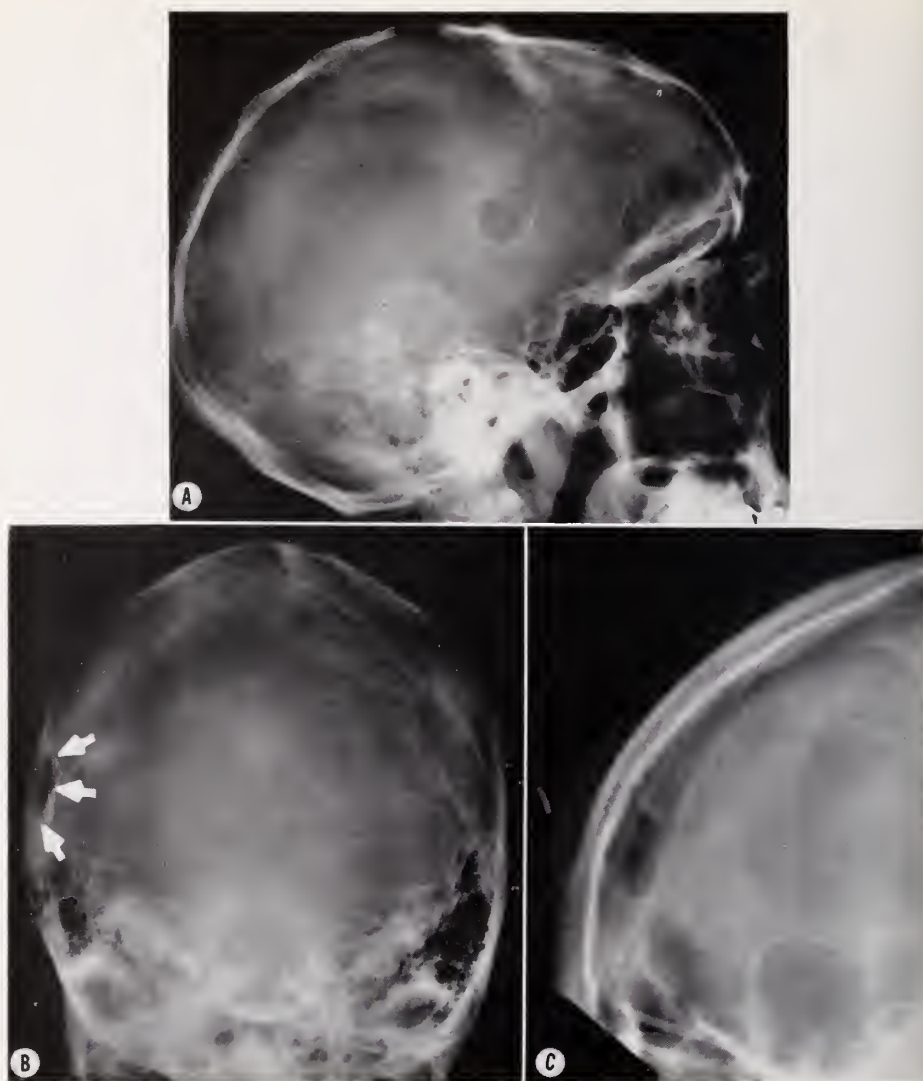
DISCUSSION

See Discussion after Case No. 233.

ACKNOWLEDGMENT

The editors wish to thank Dr. S. Adler and Dr. R. J. Greenberg of the Good Samaritan Hospital, Suffern, N. Y., for permission to use this case.

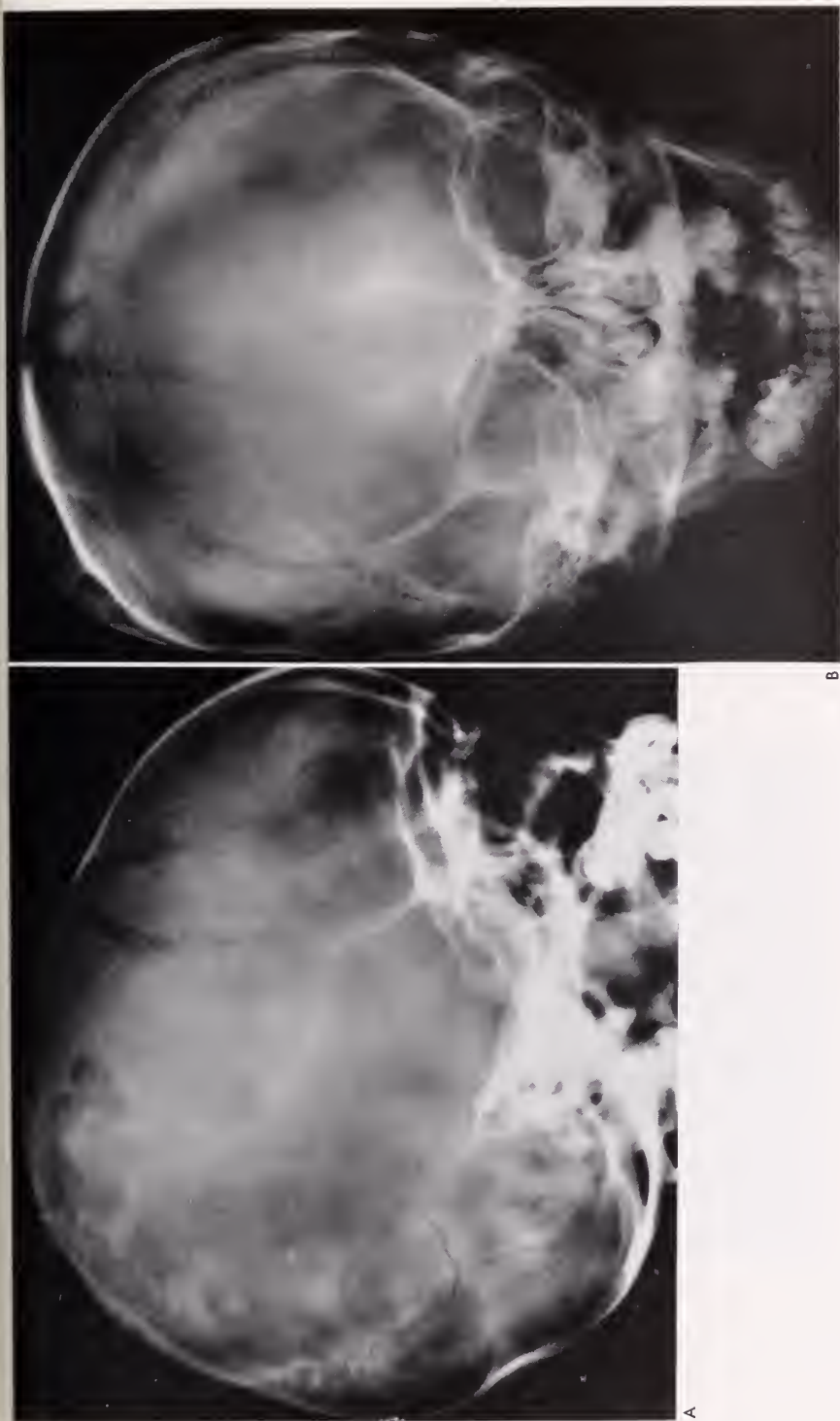
From the Department of Radiology, The Mount Sinai Hospital, New York, N. Y.



Case 228, Fig. 1A. Lateral view of the skull reveals a sharply demarcated 2 cm in diameter, round, lucent defect in the parietal bone on the right side. The inferior border of this defect is sharply delineated with a sclerotic margin. The superior portion is less sharply demarcated in this projection.

Case 228, Fig. 1B. Towne's view of the skull again reveals the sclerotic margin bordering the defect medially (arrows). The inner table appears intact. The pineal is in the midline.

Case 228, Fig. 1C. Tangential view reveals the soft tissue component within the scalp marked by a lead marker. The margination is again well demonstrated.



Case 229, Fig. 1A. Lateral projection of the skull reveals a well-circumscribed, scalloped, lucent defect in the superior portion of the right parietal bone. There is no definite surrounding sclerosis. Within the center of the lesion there is a small triangular island of increased density.

Case 229, Fig. 1B. The lesion occupies the diploic space of the superior portion of the right parietal bone with bulging of the tables. There appears to be a septate density traversing the center of the lesion.

CASE NO. 229

This 59 year old male, who was in good general health, sought medical advice because of mild trauma to the head. Radiographic examination of the skull was advised. This revealed no fractures but a large, well-circumscribed scalloped lucent defect was noted in the right parietal bone (Fig. 1). There was no definite surrounding bony sclerosis. Within the center of this lucent lesion, there was a small triangular island of increased density. In the frontal projection, the lesion was noted to occupy the diploic space with bulging of the tables. Surgical examination was performed and a large intradiploic dermoid cyst was found. The outer table was noted to be fragmented and the inner table almost completely destroyed. The dura was intact.

Case Report: DERMOID CYST—INTRADIPLOIC WITH ERODED BONY TABLES.

DISCUSSION

See Discussion after Case No. 233.

CASE NO. 230

A 3 month old male infant was admitted to the hospital for excision of a small mass in the anterior fontanel. A small bluish swelling was noted at birth located on the right aspect of the fontanel near its anterior margin. It seemed to fluctuate in size and to enlarge when the infant cried. On examination, the fontanel itself was soft and pulsated normally. The mass was firm and measured 1 cm in di-



Case 230, Fig. 1. Lateral projection of the skull reveals no bony abnormalities. In the frontal region at the anterior portion of the fontanel, there is a localized pea-sized soft tissue swelling poorly made out in the reproduction.

ameter and could not be reduced in size by compression. It seemed fixed to the deeper structures. The remainder of the examination was within normal limits.

Radiographic examination of the skull showed a pea-sized soft tissue swelling in the region of the anterior fontanel. The surrounding bone was intact (Fig. 1).

At surgery, the mass was separated by sharp dissection and was noted to be attached to the underlying dura over the sagittal sinus. The lesion was excised without damage to the sinus. It was noted to be cystic and to contain grayish sebaceous material and hair. Histological examination confirmed the impression of a dermoid cyst.

Case Report: DERMOID CYST OF THE ANTERIOR FONTANEL.

DISCUSSION

See Discussion after Case No. 233.

ACKNOWLEDGMENT

The editors wish to thank Dr. R. J. Greenberg of the Good Samaritan Hospital, Suffern, N. Y., for permission to use this case.

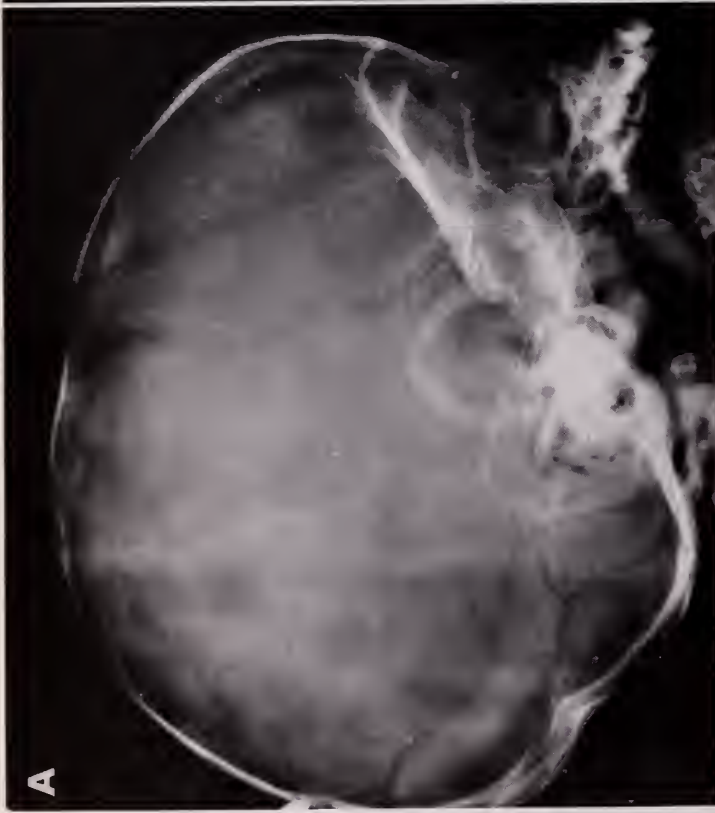
CASE NO. 231

This 8 month old girl, the product of a full-term normal pregnancy, was well until 2 months of age, when the mother noted a lump on the baby's head. There was no history of trauma and the child appeared to be in good general health. No increase in size was noted over the six-month period of observation. Physical examination was normal except for a soft nontender swelling, 2 cm in diameter, occupying the middle of the anterior portion of the anterior fontanel. Radiographic examination of the skull revealed a sharply delineated midline lucent defect in the posterior portion of the frontal bone at the anterior fontanel (Fig. 1). A well-defined soft tissue swelling was noted in the overlying scalp. The clinical and radiographic findings suggested a dermoid cyst within the anterior fontanel. The lesion has not as yet been verified histologically.

Case Report: DERMOID CYST OF THE ANTERIOR FONTANEL WITH ERODED BONY MARGINS.

DISCUSSION

See Discussion after Case No. 233.



Case 231, Fig. 1A. Lateral radiograph of the skull reveals a sharply delineated, lucent defect in the posterior portion of the frontal bone in continuity with the anterior fontanel. There is associated soft tissue swelling within the soft tissues of the scalp, not well appreciated in the reproduction.

Case 231, Fig. 1B. Frontal projection reveals the sharply delineated anterior margin of the previously described defect (arrows). It is noted to be exquisitely placed within the midline in continuity with the fontanel. There is an associated metopic suture of the frontal bone.



Case 232, Fig. 1A. Lateral view of the skull reveals a sharply delineated lucent defect within the posterior portion of the right parietal bone. There is a thin rim of dense sclerosis around the entire lesion. The remainder of the bones of the calvaria appears normal.

Case 232, Fig. 1B. Frontal view of the skull again reveals the lesion to be well circumscribed (arrows).

CASE NO. 232

A 4 month old infant came to medical attention because of a progressively enlarging mass in the right parietal region of the skull. The mother stated that two and one half months prior to that time she had noted a small hard nontender lump. There was progressive increase in size. On examination, a 3 cm firm immovable nontender mass was noted in the right parietal area. The remainder of the examination was within normal limits.

X-ray examination of the skull showed a defect in the right parietal region with smooth sclerotic margins and ballooning of both the inner and outer tables



Case 232, Fig. 1C. Tangential view reveals the lesion to occupy and expand the diploic space. The associated soft tissue swelling is well made out (arrows).

(Fig. 1). The appearance suggested an intradiploic dermoid cyst. Radiographic survey of the skeleton was otherwise normal.

At surgery, the periosteum was stripped from the mass and the outer table of the skull was noted to be extremely thin. Pinkish-gray firm tissue was found as the outer table was rongeuired. The entire tumor was removed by curettage and a markedly thinned inner table was also noted. The surgeon described extension of the tumor tissue through the inner table in a small area but the dura was not involved. Histological examination of the tumor revealed fibrous connective tissue with occasional multinucleated cells and patchy fragments of osteoid, interpreted as fibrous dysplasia.

Case Report: FIBROUS DYSPLASIA OF THE SKULL.

DISCUSSION

See Discussion after Case No. 233.

ACKNOWLEDGMENT

The editors wish to thank Dr. R. J. Greenberg of the Good Samaritan Hospital, Suffern, N. Y., for permission to use this case.

CASE NO. 233

A 30 year old female noted tenderness and headache in the right frontal region.

General physical examination was normal. Radiographic examination of the skull revealed a 2 cm rounded defect involving both tables of the right frontal bone. The edges were beveled and scalloped and there was no surrounding sclerosis. The remainder of the skeleton and the chest was normal. The diagnosis of eosinophilic granuloma was suggested. A biopsy was performed and this was confirmed histologically. The lesion was subsequently excised.

Case Report: EOSINOPHILIC GRANULOMA OF THE SKULL.

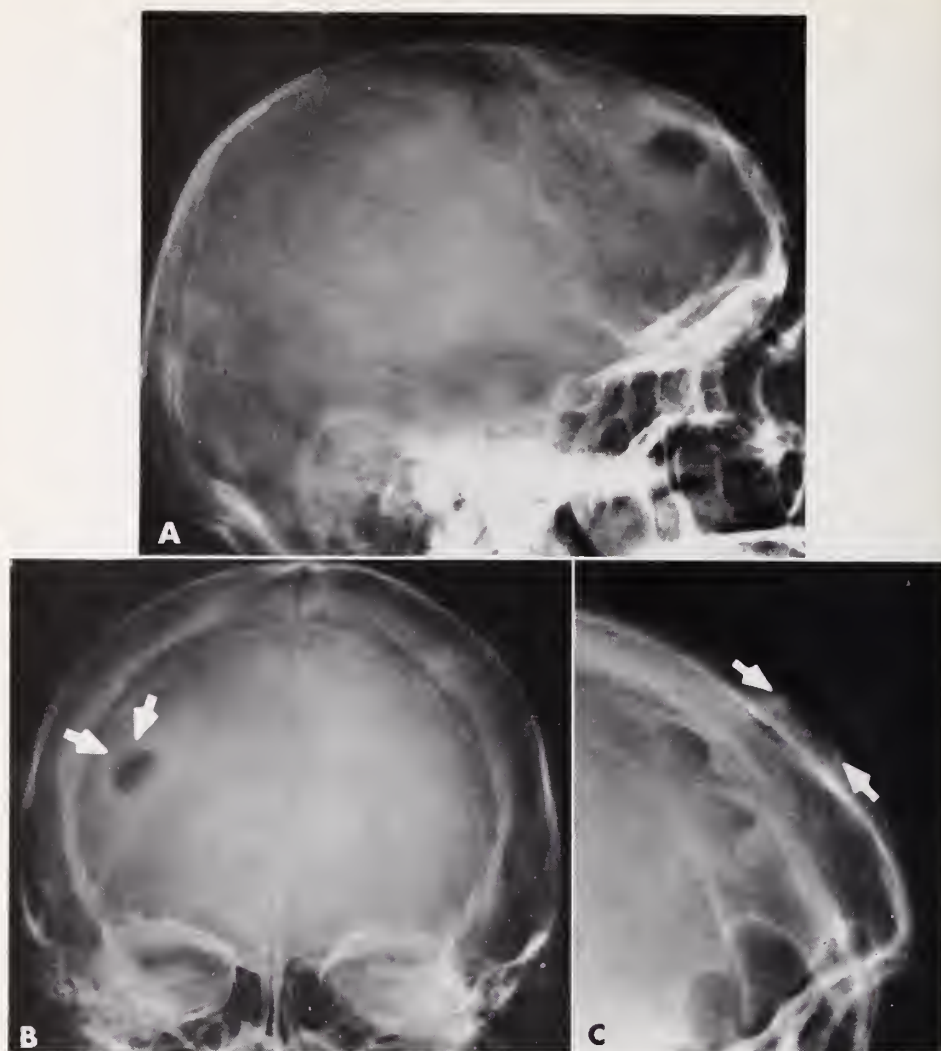
ACKNOWLEDGMENT

The editors wish to thank Dr. P. Keating and Dr. R. J. Greenberg of the Good Samaritan Hospital, Suffern, N. Y., for permission to use this case.

DISCUSSION OF CASES NO. 228 TO NO. 233

Cases No. 228 to No. 233 are discussed together as a group of benign calvarial lesions with similar radiographic features.

Cases No. 228 to No. 231 represent examples of dermoid cysts. Terminology for this type of lesion is imprecise and other terms frequently used include: epidermoid inclusion cyst, epidermoidoma, pearly tumor, and cholesteatoma. It is generally agreed that when such dermal contents as hair and sebaceous material are identified, the lesion should be classified as a dermoid cyst; when these structures are not present, the term epidermoid inclusion cyst or epidermoidoma is more applicable (1). Radiographically, the classical appearance is that of a lesion which occupies the diploic space with expansion and erosion of the bony tables. The lesion generally grows slowly and symmetrically producing a round, sharply demarcated bony defect surrounded by a thin rim of bone of increased density. These features are well demonstrated by Case No. 228. As the lesion grows within the diploic space, the tables which first are expanded then become eroded. Only one of the tables may be eroded at first with fragmentary loss of the other. When such a lesion is seen *en face* in this stage of development, the residual fragments of bone create a mottled density within the larger lucent zone resembling a sequestrum. This feature is well seen in Case No. 229. Cases No. 230 and No. 231 are examples of dermoid cysts which presented as soft tissue swellings of the scalp within the anterior fontanel. At operation, the lesion in Case No. 230 extended through the fontanel down to the sagittal sinus but did not involve the surrounding bone. Case No. 231, although as not yet confirmed histologically, most likely represents a similar but larger lesion which has eroded the adjacent bony margins. Rather than representing simple dermoid cysts,



Case 233, Fig. 1A. Lateral view of the skull reveals a well margined, scalloped lucent defect within the right frontal bone. There is no evidence of surrounding sclerosis. The remainder of the bones appears normal.

Case 233, Fig. 1B. Examination in the postero-anterior projection reveals the defect to be beveled especially superiorly (arrows).

Case 233, Fig. 1C. Tangential view reveals the lesion to occupy the entire thickness of the calvaria (arrows).

both lesions may actually represent congenital dermal sinuses, despite the fact that these are usually reported in the posterior fossa (2).

Case No. 232 represents a small well-demarcated area of fibrous dysplasia of the calvaria with no other skeletal manifestation. Because of its localized nature,

the radiographic appearance in this case cannot be differentiated from dermoid cyst. Fibrous dysplasia usually involves the calvaria in a more diffuse characteristic fashion, often in association with other skeletal lesions. Such cases present no special problems of differential diagnosis.

Case No. 233, an eosinophilic granuloma of the skull, presents the characteristic roentgen features of a so-called "punched out" lesion. The bony margins are smooth, beveled, and somewhat scalloped. No sclerosis is apparent in this case, although occasionally this feature can be present (3, 4).

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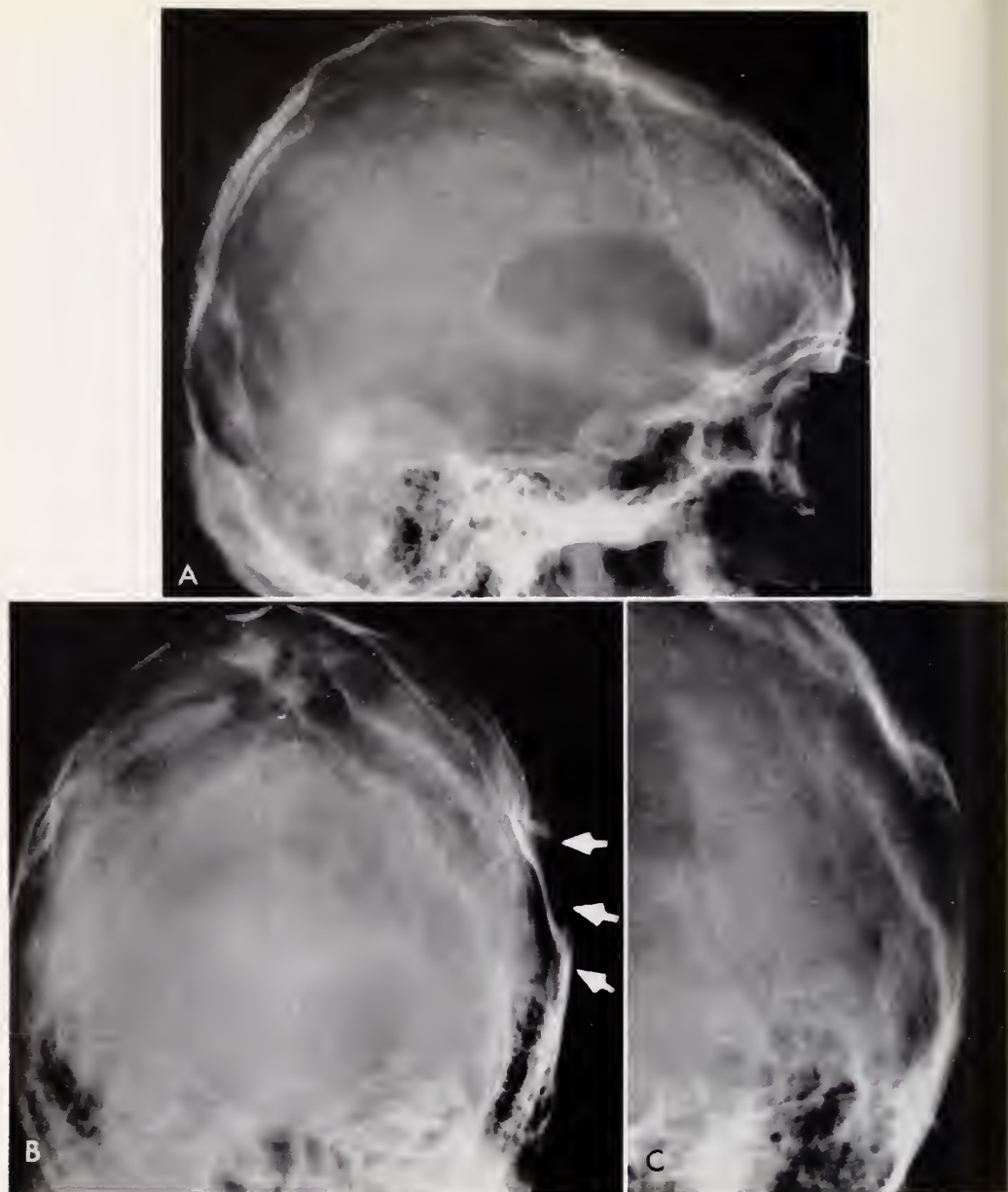
CASE NO. 234

A 30 year old right-handed male was involved in an automobile accident and sustained injury to the left side of the head with a small scalp laceration. A transient loss of consciousness occurred. Four weeks following the injury he still complained of severe localized pain in the left frontotemporal area and had episodes of severe generalized headache. Past history revealed that twelve years earlier he had sustained a minor head injury for which radiographic examination of the skull was performed. A small "bone cyst" in the left temporal region was described to the patient by his physician but no fracture was found. The radiographs are not presently available.

On examination, a small healed laceration of the scalp was noted in the left temporal region together with marked tenderness of the bone. There was a suggestion of asymmetry of the head with bulging of the left temporal area. The remainder of the examination was normal.

Radiographic examination of the skull revealed a 4×6 cm radiolucency in the left temporoparietal region which expanded and thinned the outer table (Fig. 1). The inner table was not definitely identified but the possibility of an intradiploic process bulging both tables could not be excluded. The clinical and radiographic impressions at that time were 1) cerebral concussion characterized by a transient period of unconsciousness followed by a postconcussion syndrome, and 2) an expanding lesion involving the temporal bone exact nature undetermined but a dermoid tumor to be considered. Carotid angiography was recommended for further evaluation.

Left carotid angiography revealed the pericallosal artery to be displaced 1 cm to the right in its most anterior portion. In the region of the temporal defect the smaller vascular radicles did not reach the thinned bone but again the presence or absence of the inner table was not definitely established; therefore, the significance of the relationship of the vascular supply to the bone was not



Case 234, Fig. 1A. Lateral view of the skull reveals a large oval lucent defect measuring 4×6 cm in diameter. The margins are sclerotic.

Case 234, Fig. 1B. In the Towne's projection the external table is thinned and bulges outward (along arrows). The inner table is not definitely identified in the region of the lesion.

Case 234, Fig. 1C. Tangential view reveals similar findings to better advantage.

appreciated. Nevertheless, the findings pointed to the presence of a space-occupying lesion on the left side and a craniotomy was performed.

At operation, the temporal bone was markedly thinned and expanded. There was no diploic space or inner table. Bulging dura was encountered immediately

beneath the bone. Insertion of a needle into the center of the bulge produced approximately 60 cc of thick, dark red blood. There were clearly defined outer and inner membranes of a chronic subdural hematoma and these were carefully excised. A small collection of clear fluid was encountered beneath the inner membrane. The temporal lobe, which had been compressed, expanded to reach the dural surface at the conclusion of the procedure. The neurosurgical findings were interpreted as a chronic subdural hematoma with a possible underlying arachnoid cyst.

Histological examination of the membranes revealed evidence of a recent chronic subdural hematoma. Portions of the membranes were very old, however, and contained some pigment deposits. The pathologist interpreted the findings to indicate a recent hemorrhage superimposed on the residua from an old hemorrhage, the latter possibly having resulted in a subdural hygroma. No discrete subarachnoid membrane was identified. The postoperative course was unremarkable and follow-up examination six months after surgery revealed no neurologic abnormality.

DISCUSSION

A number of chronic space-occupying processes have been reported in association with overlying calvarial defects in the middle cranial fossa. These include arachnoid cyst, chronic subdural hematoma, subdural hygroma, cerebral glioma, cerebral agenesis and neurofibromatosis (1 to 3). (Pulsating leptomeningeal cyst secondary to major skull fracture does not fall into this group (4).) The bony abnormality is characteristically temporal or parietal in location and features a thinned and expanded bony area of variable size with smooth sclerotic margins. There may be associated enlargement of the entire middle cranial fossa with bulging floor and elevated lesser sphenoid wing, and in some cases the fossa is enlarged in the absence of a localized bone defect.

Arachnoid cyst is an entity which is poorly understood. In its simplest form, a collection of cerebrospinal fluid is present covered by normal leptomeninges and often communicates with the general subarachnoid space. The origin of such a collection is unknown but some cases may be congenital in nature and associated with cerebral agenesis (3). A number of other theories have been advanced including trauma, inflammation, and bleeding, but none of these can be verified from the pathophysiological standpoint (5). In addition, neurosurgical descriptions are often fragmentary and imprecise. Chronic subdural hematoma may be encountered independently or in association with an arachnoid cyst. In the latter case, it can be argued that the cyst predisposed to bleeding. In the former case, it is possible that an underlying cyst was distorted or obliterated by the hemorrhage and thus not recognized surgically or histologically. Acute subdural hygroma usually follows trauma without hemorrhage (6) but chronic subdural hygroma is believed to be the end result of a chronic subdural hematoma after the bloody fluid has been resorbed.

In the case presented, the recent chronic subdural hematoma may have been superimposed on a subdural hygroma which followed an old hemorrhage—suggested by the pathological findings, or an arachnoid cyst—suggested by the

neurosurgical findings. Either of these two sequences could explain the clinical and radiological features.

Case Report: TEMPORAL BONE DEFECT WITH RECENT CHRONIC SUBDURAL HEMATOMA AND POSSIBLE UNDERLYING SUBDURAL HYGROMA OR ARACHNOID CYST.

ACKNOWLEDGMENT

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Hemolytic Anemia as a Complication of Carcinoma: Case Report and Review of the Literature

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There have been numerous reports on the pathogenesis of anemia in neoplastic disease. Most cases on investigation are found to be associated with a combination of blood loss, decreased red cell production, and increased red cell destruction. Although any or all of these mechanisms may vary in severity in any one case, markedly increased destruction (hemolysis) of red cells is not commonly noted. Active hemolysis is occasionally noted in leukemia and lymphoma, but only rarely has it been described in carcinoma. It was felt worth while to report a case of severe hemolytic anemia associated with carcinoma of the pancreas.

CASE REPORT

C.H., a 52 year old retired cabinetmaker, was admitted to the Medical College of Virginia Hospital on November 13, 1962, complaining of low back pain of three months' duration.

On October 14, 1962, he was admitted to another hospital for the same complaint. Physical examination was unrevealing. Laboratory tests revealed a hemoglobin of 11.4 Gm%; the red cells showed hypochromia and anisocytosis. Repeat hemoglobin on October 27, 1962, was 10.5 Gm%. Urine culture showed abundant *Staphylococcus aureus*, and intravenous pyelography showed two calculi in the left middle calyx without hydronephrosis.

The patient was treated with bed rest, back board, analgesics, and chloramphenicol, 500 mg four times daily for one week. At the time of discharge, he was given a ten days' supply of sulfisoxazole, 1 Gm three times a day. However, there was only minimal improvement in his back pain.

Following discharge, his back pain became increasingly more severe, and he noted pain in his left posterior rib cage, along with nausea, vomiting, abdominal cramping, and a gradual weight loss. Past history revealed an allergic skin rash to an unknown "sulfa" drug many years previously, but no rash while taking the sulfisoxazole. He was almost edentulous and admitted to moderately severe alcoholism and a poor diet.

Physical examination showed a well-developed, well-nourished male com-

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plaining bitterly of back and rib pain. Blood pressure was 160/80, pulse 90, respirations 18, and temperature 37.0°C. He presented an unkempt appearance and was almost edentulous from severe dental caries. His tongue was smooth, but not tender or inflamed. The mucous membranes were pale. No icterus was evident. His abdomen was flat, and the liver and spleen were not palpable. There was a suggestion of a hard, irregular mass in the epigastric and left upper quadrant areas, which moved somewhat with respiration. Examination of the skeleton revealed only a nontender lumbar scoliosis with mild diffuse tenderness of the left posterior ribs and upper lumbar spines.

Admission blood counts showed a hemoglobin of 5.8 Gm%, white blood cell count of 10,750/cu mm, and platelet count of 225,000/cu mm. Differential white cell count showed 86% neutrophils, 1% eosinophils, 1% basophils, 8% lymphocytes, and 4% monocytes. The red blood cells were normocytic, normochromic, with numerous polychromatophilic macrocytes. The reticulocyte count was 22%, and red blood cell indices showed a MCV of 110 cu μ , MCH of 36 μ g, and MCHC of 33%. The neutrophils showed increased lobulation, with 2% having six or more lobes, 12% with five lobes, 40% with four lobes, and 46% with three lobes or less. Sternal bone marrow aspiration on November 15, 1962, revealed a hypercellular specimen with normal iron stores and normal platelet production. Myeloid to erythroid ratio was 0.7. There were 4% plasma cells, 4% reticulum cells, 5% lymphocytes, 36% cells of the granulocytic series, and 51% cells of the red cell series with minimal megaloblastoid changes. No tumor cells were seen. Further serial blood studies are shown on Table I. Of importance is the observation that later blood smears showed severe anisocytosis, poikilocytosis, spherocytes, red blood cell fragments, severe scalloping of the red cell borders, and an occasional normoblast. Numerous polychromatophilic and non-polychromatophilic macrocytes were also seen in abundance.

The following tests were normal: urinalysis, urine culture, fasting blood glucose, urea nitrogen, serum proteins, acid phosphatase, serologic test for syphilis, electrolytes, bleeding and clotting times, thymol turbidity, and direct and indirect bilirubin. Alkaline phosphatase was 3.0 B.L. units (normal 0.8 to 2.9 B.L. units), prothrombin time 13 seconds (control 11 seconds), and bromsulfalein retention of 10% after 45 minutes (normal 0 to 4%).

A chest x-ray was negative. A splenic scan using heated, Cr⁵¹-labeled red cells on November 29 showed no splenomegaly. On December 4, following intravenous injection of colloidal Au¹⁹⁸, a normal liver scan was obtained. Multiple x-rays of the urinary collecting system showed only a moderate degree of bilateral hydronephrosis. The lumbar spines showed degenerative joint changes, and no bone lesions were noted on skeletal survey. An upper gastrointestinal series on December 1 showed a polypoid lesion along the greater and lesser curvature aspects of the antrum of the stomach with partial prepyloric obstruction.

The patient was initially treated with bed rest and analgesics without

TABLE I
Serial Blood Studies on Patient C.H.

Date	Hemoglobin (Gm%)	Hema- tocrit (%)	White Blood Count (cu mm)	Reticulo- cytes (%)	Direct Bilirubin (mg%)	Indirect Bilirubin (mg%)	Blood Urea Nitrogen (mg%)	Trans- fusions (units)
Oct. 15	11.4	—	14,600	—	—	—	14	0
Oct. 27	10.5	—	10,500	—	—	—	—	0
Nov. 14	6.2	—	9,700	—	0.05	0.35	11	0
Nov. 15	5.9	18	10,750	22	—	—	—	0
Nov. 20	4.9	—	9,150	—	—	—	—	0
Nov. 21	—	—	—	—	0.3	1.0	—	0
Nov. 26	4.5	15	—	59	0.9	1.5	—	0
Nov. 28	4.5	15	15,150	66	—	—	—	2
Nov. 29	7.2	22	—	—	—	—	—	0
Nov. 30	6.0	20	—	—	—	—	59	2
Dec. 1	9.2	30	—	—	—	—	—	2
Dec. 2	8.8	29	—	—	—	—	—	0
Dec. 3	9.5	29	—	41	—	—	60	0
Dec. 4	9.6	28	—	38	4.9	3.5	84	2
Dec. 6	9.6	30	—	—	5.0	3.2	85	0
Dec. 7	12.4	—	17,600	—	—	—	78	4
Dec. 8	14.8	—	19,800	—	—	—	100	1
Dec. 10	10.2	—	23,300	—	22.4	19.2	150	2

TABLE II
Characterization of Hemolytic Process in Patient C.H.

Test	Result	Normal or Control
Hemolytic Index	224	11-22
Osmotic Fragility	0.70 to 0.36	0.48 to 0.36
Coombs Test	negative	negative
Cold Agglutinins	negative	negative
Warm Agglutinins	negative	negative
Acid Hemolysin (Ham)	negative	negative
Donath-Landsteiner	negative	negative
Cross-matching	normal, uncomplicated	
Serum B ₁₂ (E. gracilis)	1462 $\mu\text{g}/\text{cc}$	250-800 $\mu\text{g}/\text{cc}$
Serum Folic Acid (Strep. faecalis)	3.0-4.0 $\text{m}\mu\text{g}/\text{cc}$	2-6 $\text{m}\mu\text{g}/\text{cc}$
Serum Protein Fractionation	A: 3.7 G: 2.6	same
Hemoglobin Electrophoresis	A hemoglobin	A hemoglobin
Sulfisoxazole Hemolysis Test	negative	negative
Tumor Hemolysins or Tissue Antibodies	none	negative

response. Serial blood studies showed evidence of a marked hemolytic process for which no cause could be ascertained (Table II). By the time the abnormal gastrointestinal x-rays were obtained, the patient was severely anemic, icteric, disoriented, and had severe nausea and vomiting. On December 7, he underwent exploratory laparotomy at which time a large fixed mass was found deep in the epigastrium continuous with the pancreas and porta

hepatis, causing duodenal obstruction. The liver was riddled with metastatic deposits. The polypoid lesion of the stomach was noted, but was not continuous with the main tumor mass. A palliative gastrojejunostomy was performed. Postoperatively, he did poorly and died on December 11 with increasing azotemia, icterus, and coma. Although there was minimal blood loss before, during, and after the operation, he required transfusion of 15 units of whole blood and packed cells to maintain a hemoglobin of at least 9 Gm% in the last two weeks of his life.

Autopsy was performed thirteen hours after death. Important findings were limited to the abdomen. The large mass was again noted continuous with the head of the pancreas, porta hepatis, mesenteric nodes, and surrounding the inferior vena cava and both kidneys. There was complete obstruction of the cystic and common hepatic ducts by the tumor. The liver was markedly enlarged and was studded with metastases. The spleen weighed 250 Gm and showed numerous infarcts on cut section. Microscopic sections revealed the tumor to be a mucus-secreting adenocarcinoma of the pancreas. The polypoid lesion in the stomach was felt to be an area of metastasis, although it could not be said for certain that it was not the primary focus. Metastases were also noted in the adrenals, mesenteric and carinal lymph nodes, and in sections of the lumbar vertebrae. Considerable necrosis was noted in the hepatic metastases. There was no evidence of fatty infiltration or cirrhosis. The spleen showed a moderate degree of reticulo-endothelial hyperplasia, and minimal amounts of hemosiderin. No areas of extramedullary hematopoiesis were noted. The kidneys showed moderate hydronephrosis secondary to ureteral obstruction by tumor, and sections of the parenchyma showed no areas of inflammation. The final diagnosis was adenocarcinoma of the head of the pancreas, widespread metastases, and terminal bronchopneumonia.

SPECIAL STUDIES

In an effort to define the underlying mechanism for the patient's severe hemolytic process, extensive studies were undertaken (Table II). His blood was easily cross-matched (group O Rh positive), and his serum gave negative results with a panel of red cells containing all major and most minor red blood cell antigens at room temperature and at 37°C., in saline and albumin, with gamma and non-gamma globulin Coombs serum, and with normal and trypsinized red cells. In addition, there were no transfusion reactions to any of the 15 administered units.

Because of the history of skin allergy to a sulfa drug in the past and recent treatment with sulfisoxazole, a hemolytic drug reaction was suspected. The patient's red blood cells were washed three times in saline, and incubated in a saline solution of sulfisoxazole in a final concentration of 20 mg%. Washed cells of the patient were also resuspended in his own serum with added drug in the same final concentration. Control cells were suspended in saline, the patient's serum with added guinea pig complement, and with normal serum, with and without sulfisoxazole. All tubes were incubated at 37°C.

for fifteen to thirty minutes and observed for agglutination, lysis, and positive Coombs reaction. All tubes were negative.

Because of previously reported work on human and animal tumors, an effort was made to detect the presence of tissue hemolysins or abnormal tissue antibodies. A small tumor nodule was removed from the liver at the time of exploratory laparotomy and kept frozen until used. The nodule was ground for fifteen minutes in ten times its weight of saline, centrifuged at 5000 rpm for thirty minutes at 5°C., the supernatant removed and frozen until used. Red cells fully compatible with the patient's serum and normal serum were made to a 1% suspension in saline with and without prior trypsinization. One-half cubic centimeter of tumor homogenate supernatant was then incubated at 37°C. with one cubic centimeter of the red cell suspension with and without addition of purified guinea pig complement for periods of from 60 to 150 minutes. No agglutination, lysis, or positive Coombs reaction was seen in any of the tubes. The incubated red cells were then incubated with normal serum or the patient's serum for one hour at room temperature and 37°C., and again observed for agglutination, lysis, or positive Coombs reaction. Again, all tubes were negative.

COMMENTS

It was felt that there was adequate documentation of severe hemolysis on the basis of a markedly increased hemolytic index (1), increased transfusion requirement, increased osmotic fragility with aniso- and poikilocytosis, spherocytosis, fragmented and bizarrely-shaped red cells with macrocytic changes, extremely high reticulocyte count, and severe erythroid hyperplasia of the bone marrow.

An allergic hemolytic reaction to sulfisoxazole was considered, but the patient's hemoglobin level was falling before this drug was started and continued to fall for one month after it was discontinued. Attempts to document *in vitro* hemolysis with the drug were unsuccessful.

At no time was there any gross blood loss, and although stool and gastric aspirates were positive for blood on testing with guaiac reagent, gross examination of all excreta for fresh blood or melena was negative. In spite of this and the minimal blood loss at the time of surgery, he had a marked transfusion requirement during the last two weeks of life.

The consistently high white blood cell count, normoblastemia, immature granulocytes, and abnormally shaped red cells suggested extramedullary hematopoiesis as a factor in the patient's anemia. At autopsy this was not found despite a careful search. The involvement of the bone marrow with tumor, probably by direct spread, was probably responsible for some of the above changes (2).

Auto-immune factors causing the hemolysis were considered, but extensive testing with various cross-matching techniques, chemically altered red cells, Coombs techniques, and incubation with tumor extract revealed no evidence of tissue hemolysins or unusual antibodies by the techniques used.

It was felt that the megaloblastoid changes were due to increased demand for, and reduced supply of nutriment during the course of acute hemolysis. However, serum levels of folic acid and vitamin B₁₂ were not low, and folic acid, in a dose of 100 μ g per day by mouth, did not alter the hemolytic process or the megaloblastoid picture.

Thus, it was felt that hemolysis was the main factor in the patient's anemia, but the mechanism for the increased red cell destruction was not clear.

DISCUSSION

The anemia of malignancy has received considerable attention in the recent literature. Before the advent of radioactive tracers, it was largely believed that the anemia was the result of combinations of blood loss, poor nutrition, and other "toxic" factors produced by the cancer itself. However, with the use of tracers in studying iron and red cell kinetics in malignancy has grown an appreciation of definite shortening of red cell survival in many cases (3-6). In addition, a review of the literature has uncovered numerous cases of hemolysis associated with lymphoma and leukemia (10, 12), but only fifteen case reports where carcinoma was associated with clinically recognized hemolysis (Table III) (7-19).

A review of these fifteen cases reveals that twelve have involved the gastrointestinal tract (pancreas included). While seven different sites were noted, all but four of the fifteen cases were histologically adenocarcinoma, as was the present case. Including the present case, ten of the eleven autopsied cases showed reticulo-endothelial hyperplasia and/or increased hemosiderin in the liver or spleen. Eleven cases had bony metastases, and six had extramedullary hematopoiesis. Since this latter condition is in itself associated with a moderate shortening of red cell survival, it is possible that some of these cases had evidence of hemolysis on this basis alone.

Experimental data on animals with transplanted tumors (20-24) has shown that reticulo-endothelial hyperplasia and increased hemosiderin in the liver and/or spleen are commonly seen. It has been postulated that this increased reticulo-endothelial activity is due either to a foreign protein or toxic effect (21), or as an attempt at a type of homograft rejection (24) by the host.

It has been suggested that the presence of necrotic tissue in the malignancy may be a stimulus to increased reticulo-endothelial activity. Extracts of necrotic animal and human tumor have also been noted to be hemolytic for red blood cells *in vitro* (25-27). Using extracts of necrotic and non-necrotic tumor in hamsters, Sherman (20, 21) found that normal animals injected with cell-free extracts of necrotic tumor showed the development of significant anemia, and at autopsy showed splenomegaly and increased bone marrow activity. Animals injected with cell-free extracts of non-necrotic tumor showed no significant hematologic or autopsy findings. It is thus possible that the considerable necrosis noted in the autopsy of the present case may have had a direct relationship to the reticulo-endothelial hyperplasia also seen and to the development of hemo-

TABLE III
Collected Cases of Carcinoma and Hemolytic Anemia

Author and Date	Reference Number	Lowest Hemoglobin (Gm% or % of Normal)	Highest Reticulocyte Count (%)	Normoblasts (Per 100 WBC)	Immature WBC in Blood	Spherocytosis	Anisopoikilocytosis	Macrocytic RBC Changes	RBC Osmotic Fragility	Atypical Serum Antibodies	Bone Marrow Metastases	Extramedullary Hematopoiesis	Reticuloendothelial Hyperplasia	Reticuloendothelial Hemosiderin	Primary Site of Tumor
Seeman, Krasnopolski—1926	16	12%	—	many	yes	—	yes	yes	—	—	yes	yes	yes	yes	stomach
Faulds, MacKay—1927	18	28%	—	7	yes	no	yes	yes	—	no	yes	no	yes	yes	pancreas
Waugh—1936	19	5.5	6	0	yes	—	yes	no	incr.	—	yes	—	—	—	prostate?
Waugh—1936	19	6.4	8	7	yes	—	no	yes	incr.	no	yes	yes	yes	yes	breast
Caroli, Laverne—1937	17	30%	—	16	yes	yes	yes	no	incr.	no	yes	no	no	yes	stomach
Lucy—1939	8	26%	45	125	yes	yes	yes	—	incr.	no	yes	no	no	yes	lung
Holmes, McCall—1940	9	37%	6	3	yes	no	yes	no	norm.	no	yes	yes	yes	yes	stomach
Holmes, McCall—1940	9	10%	30	0	yes	no	yes	no	norm.	no	no	no	no	yes	stomach
Davis—1944	10	36%	28	0	no	no	no	yes	norm.	no	no	no	yes	yes	pancreas
Jones, Tillman—1945	15	4.5	20	0	no	yes	—	—	incr.	yes	no	—	—	—	ovary
Tötterman—1946	11	40%	5	4	yes	—	—	—	norm.	—	—	—	—	—	stomach
Stats <i>et al.</i> —1947	12	24%	87	370	—	yes	yes	—	incr.	yes	—	—	—	—	colon?
Frandsen—1949	11	33%	16	17	yes	no	yes	—	norm.	no	yes	yes	no	no	pancreas?
Hogman—1953	13	33%	5	0	yes	no	no	no	incr.	no	yes	yes	no	yes	stomach
Frumin <i>et al.</i> —1954	14	6.7	13	0	yes	yes	yes	—	norm.	yes	yes	yes	—	—	stomach
Present Case	—	4.5	66	2	yes	yes	yes	yes	incr.	no	yes	no	yes	yes	pancreas?

lytic anemia. Since shortened red cell survival seems to be fairly common in patients with disseminated neoplasm (3-6), and since tumor necrosis is common with advancing disease, the necrotic tumor tissue or some of its products may have some role in the genesis of these hematologic changes.

The production of auto-antibodies may also be associated with carcinoma and hemolytic anemia. Of the fifteen collected cases, there were atypical antibodies noted in three. One had a positive direct and indirect Coombs reaction with a "circulating antibody of auto-agglutinin nature" (14), one a titer of cold agglutinins to 1:5 (12), and one with an unusual difficulty noted in cross-matching which disappeared immediately after removal of her tumor (15), along with abatement of her hemolytic process. In a distinctly unusual case reported by Levine and co-workers (28), a woman with proven carcinoma of the stomach was found to have blood incompatible with all of 3000 random group and type-specific donors. There was no history of prior sensitizations. Only two people were found to be fully compatible with the patient's serum: her sister and a woman in South Africa who also had a similar antibody, presumably as a result of immunization through multiple pregnancies. Aliquots of the resected tumor were found to specifically absorb the antibody. The authors concluded that the patient and her sister failed to inherit from their parents a common red cell antigen, which they called J^a . However, their patient harbored the antigen in her tumor cells, probably through mutation, leading to antibody formation. Of a similar nature is the acquisition of a B-like red cell antigen in recently reported cases of carcinoma of the colon and rectum (29-31), and changes in the A antigen in various types of leukemia (32, 33) during the course of that disease. In experimental tumors, Betts and co-workers (34) found positive antiglobulin tests in a high percentage of tumor-bearing hamsters. Of those animals with positive tests eight of twelve were anemic, while no animal with a negative antiglobulin test was anemic, suggesting that the positive test precedes the anemia.

An interesting phenomenon of immunity to transplantation of tumor and hemolytic anemia in animals is the FHA (filterable hemolytic agent) of Sacks *et al.* (35). This agent, which is a replicating filterable agent, presumably a virus, produces a severe hemolytic anemia in rats. Following recovery from this hemolysis, the rats are immune not only to further hemolysis from the FHA, but also show a remarkable ability to resist successful transplantation of many different tumors. The authors are at a loss to explain this immunity, but suggest that genetic similarities between the FHA and the tumors are responsible. However, the fact that a hemolytic process is intimately associated with the phenomenon of tumor immunity suggests that there are antigenic similarities among the three systems: red cells, FHA and tumor.

That tumors can produce a "toxic" product or products has long been suggested. *In vitro* testing with extracts of tumor, but also with extracts of normal tissue, has shown agglutination and/or hemolysis of red cells from

the same, or widely different experimental animals and humans (36-39). The status of tissue hemolysins is uncertain at this time, and there are some who cast strong doubt on the entire concept (40). Such hemolysins were looked for in the present case but were not found.

An interesting and unexpected finding which appeared on collecting other cases of carcinoma and hemolytic anemia was the very high incidence of carcinomas of the gastrointestinal tract, and of adenocarcinomas of all sites. The histologic demonstration of glandular structures in these tumors, plus the histochemical demonstration of production of "colloid," "mucin," or "pseudomucin," suggest that a product of these tumors may indeed be responsible for the hemolysis. For the most part, the main component of this mucus-like material is a high molecular weight glycoprotein (41) or mucopolysaccharide. Some, but not all, of these molecules possess antigenic similarities with blood groups A, B, H and Le^a, and are the substances produced by so-called "secreters." By using immunofluorescent serum against a mucin possessing A substance activity found in ovarian cyst fluid, Glynn and Holborow (42) were able to demonstrate A substance production by the cells of an adenocarcinoma of the stomach, and traces of activity in a carcinoma of the colon. Morgan and Watkins (43) have further characterized these substances, and found that some molecules exist which have both A and Le^a activity, as well as those that have A or Le^a activity alone, or none at all. Mild acid hydrolysis of these substances produces loss of the blood group activity as measured by iso-agglutinin inhibition, but also develops *new* serologic specificity with antigenicity, and these altered substances are able to stimulate antibody formation even in individuals of the same blood groups as those from whom the original substance was derived. The antigenicity seems to reside in the sugar groups, and not in the amino acid portions, although papain or ficin digestion of these compounds also destroys their antigenicity, probably by disruption of the entire molecular structure.

Thus, there exists evidence that malignancies do produce antigenic materials which have similarities to the red cell antigens, and which are capable of altering their antigenicity without gross changes in their molecular structure. Systemic absorption of these molecules might explain the hemolytic process in those cases referred to previously: the patient with acute hemolytic anemia, cross-matching difficulty, and pseudomucinous cystadenocarcinoma of the ovary (15), who had reversal of her hemolysis following removal of the tumor, and the cases of dermoid cyst or teratoma (44) of the ovary who had hemolysis relieved by their removal, plus the unusual blood group changes referred to above, occurring mainly in patients with carcinomas of the bowel. In addition, this would explain why thirteen of the sixteen cases with hemolytic anemia and carcinoma had negative antibody tests, as these mucin-like compounds are not gamma globulins, and would not be expected to react with ordinary Coombs sera. Furthermore, it should be mentioned that antibody testing such as that done in the present case was negative when the searched-for end point was hemolysis, agglutination, or globulin

coating of the red cells. Atypical antibodies or reactions may exist which produce more subtle red cell changes, however, such as increased red cell fragility, or the peculiar red cell scalloping noted in this case and in other immune hemolytic anemias (45), which may lead to decreased survival *in vivo*.

A definite relationship seems to exist among these tumors, mucinous compounds, and red cell antigens, just as was noted for the FHA of Sacks *et al.* It is the feeling of this author that the above findings are not coincidental, and that further investigation of these systems will help to uncover some of the problems of host relationships in the various malignancies.

SUMMARY

A case of acute hemolytic anemia occurring as a preterminal complication in carcinoma of the pancreas was presented. Multiple laboratory studies failed to elucidate the mechanism involved in the hemolysis. A review of the pertinent literature on animal and human tumors and hemolytic anemia is given, along with several suggestions as to the possible mechanisms involved.

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Multiple Endocrine Adenomatosis

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Multiple endocrine adenomatosis has been defined as a distinct clinical entity (1-3). The endocrine glands most frequently involved are the parathyroids, pituitary, and pancreas. Histological studies have shown that hyperplasia as well as adenomata can be present in different endocrine glands of the same patient (2-5). Hyperplasia or adenoma of the pancreatic islet cells may be manifested by hypoglycemia with its characteristic symptomatology, or the Zollinger-Ellison syndrome (6, 7). The thyroid and adrenal glands may be involved, but only rarely are these abnormalities functional. Bronchial adenoma (8) (sometimes serotonin secreting) and lipomas (9) have been reported in association with multiple endocrine adenomatosis.

The present case is of particular interest because of the early age of onset (thirteen years), the length of personal observation (ten years), the recurrence of hyperparathyroidism due to a mediastinal parathyroid adenoma, and the presence of a fifth functioning parathyroid gland.

CASE REPORT

Patient F.S., a 30 year old female, was first seen in The Mount Sinai Hospital Endocrine Clinic in March, 1953, because of amenorrhea present since the age of thirteen, and headaches of increasing frequency for one year. Menarche occurred at the age of eleven, and the patient experienced regular menses for two years at which time they ceased suddenly. She was married at the age of twenty and was subsequently unable to conceive. Vague "arthritic pains" in the extremities had begun at the age of twenty and at age twenty-four she passed a renal calculus. In June, 1952, one year prior to her first clinic visit, the patient noted the onset of episodes characterized by sweating, nervousness, diplopia, and at times confusion, incontinence, amnesia, and loss of consciousness. These attacks usually occurred Saturday or Sunday mornings when she awoke late for breakfast. The attacks could be aborted by drinking fruit juice. In August, 1952, she was hospitalized in a psychiatric institution during an episode of confusion thought to be schizophrenic in origin.

The family history was essentially negative except for a sister who has a history suggestive of peptic ulcer but has consistently refused any medical attention.

Physical examination during her initial visit revealed a nodular thyroid and a bitemporal field defect. The genitalia, hair distribution and breasts were normal, as was the remainder of the examination.

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Pertinent laboratory evaluation disclosed the absence of urinary gonadotropins at 5 mouse uterine units. The vaginal smear was estrogen deficient. The PBI was 5.8 gamma% and the RAI uptake after 24 hours was 20%. A glucose tolerance curve was characteristic of diabetes mellitus (FBS-67 mg%, 1 hr.—192 mg%, 2 hr.—217 mg%, 3 hr.—210 mg%). X-ray examination of the skull revealed the sella turcica to be enlarged with demineralization of the dorsum sellae and the posterior clinoid processes (Fig. 1).



FIG. 1. Enlarged sella turcica with demineralization of the dorsum sellae and the posterior clinoid processes.

From August, 1953, to November, 1953, the patient received 10,000 roentgens air dose to the pituitary gland. Her headaches were markedly reduced in number and intensity, and there was no progression of her visual field defects. However, morning episodes of nervousness, sweating and confusion continued. A repeat glucose tolerance test extended to 5 hours demonstrated a low fasting level (54 mg%), followed once again by a diabetic-type curve (1 hr.—216 mg%, 2 hr.—222 mg%, 3 hr.—144 mg%, 4 hr.—106 mg%). However at the fifth hour the blood sugar level had fallen to 45 mg%, and the patient complained of nervousness and sweating. The symptoms were relieved by intravenous glucose. A 24 hour urinary 17-hydroxy-corticoid

determination was 10.1 mg. The serum calcium was 12.1 mg% and serum phosphorus 2.5 mg%.

The patient was then admitted to The Mount Sinai Hospital with the diagnosis of "multiple endocrine adenomatosis." Multiple serum calcium determinations ranged from 11.5 mg% to 12.5 mg%, with the serum phosphorus consistently below 2.8 mg%. A 24 hour urine calcium while on a Bauer-Aub diet was 700 mg. X-ray examination of the skeleton revealed diffuse osteoporosis. The lamina dura was present. Episodes of sweating, confusion and nervousness associated with low blood sugar (28-40 mg%) occurred spontaneously and were induced by a 12 hour fast.

Abdominal exploration was performed and two nodules were palpated in the distal pancreas. The right adrenal gland was also nodular to palpation. The body and tail of the pancreas was resected and on gross examination two nodules were present on each side of the pancreatic duct. The remainder of the excised gland appeared grossly normal. Microscopic examination of the pancreatic nodules demonstrated that they were islet cell adenomata. Postoperatively the patient was transiently hyperglycemic, but did not require insulin.

Six weeks after the abdominal procedure the patient was subjected to exploration of the neck. All four parathyroid glands were identified by the surgeon on the posterior aspect of the thyroid and all appeared enlarged. However the inferior parathyroid glands and the right upper gland were markedly enlarged. These three glands were removed. Pathological examination confirmed the removal of three parathyroid glands, two of which contained clear cell adenomata. Postoperatively the patient did not experience any signs or symptoms of hypoparathyroidism. The serum calcium fell to 10.6 mg% and the phosphorus rose to 3.0 mg% over a three day period.

The patient was subsequently seen in the Endocrine Clinic and repeated calcium and fasting blood sugar levels were within the normal range. In April, 1957, she experienced three bouts of renal colic associated with pyuria and hematuria. The serum calcium at this time was 11.8 mg%. An intravenous pyelogram demonstrated two stones in the pelvis of the right kidney with mottled calcification of the upper pole of the left kidney. The blood urea nitrogen was 14 mg%. The patient was readmitted to The Mount Sinai Hospital. Calcium determinations were consistently elevated to approximately 12.0 mg% with a phosphorus of 2.7 mg%. While on a Bauer-Aub diet, a 24 hour urine contained 400 mg of calcium. The patient became depressed and signed herself out against advice when she was notified that surgery was indicated.

She did not return until she experienced severe right flank pain associated with urgency and costovertebral angle tenderness and was admitted to the hospital on 5-15-59. Intravenous pyelography and cystoscopy demonstrated an obstructing stone at the right ureterovesical junction and another stone in the left ureteropelvic junction with mild hydronephrosis. Multiple serum calcium determinations were again elevated. A barium swallow (Fig. 2)

revealed a flat impression on the left lateral wall of the esophagus a short distance below the thoracic inlet. X-ray examination of the upper gastrointestinal tract was normal. The 24 hour urinary 17-hydroxy-corticoids was 9.9 mg.

On 5-26-59, a left ureteropyelolithotomy was performed. The operative and postoperative course were uneventful. On 6-22-59, a neck exploration was again performed and a parathyroid adenoma was found between the esophagus and prevertebral space at the base of the neck in the midline. (It should be noted that at the original exploration of the neck four parathyroid glands

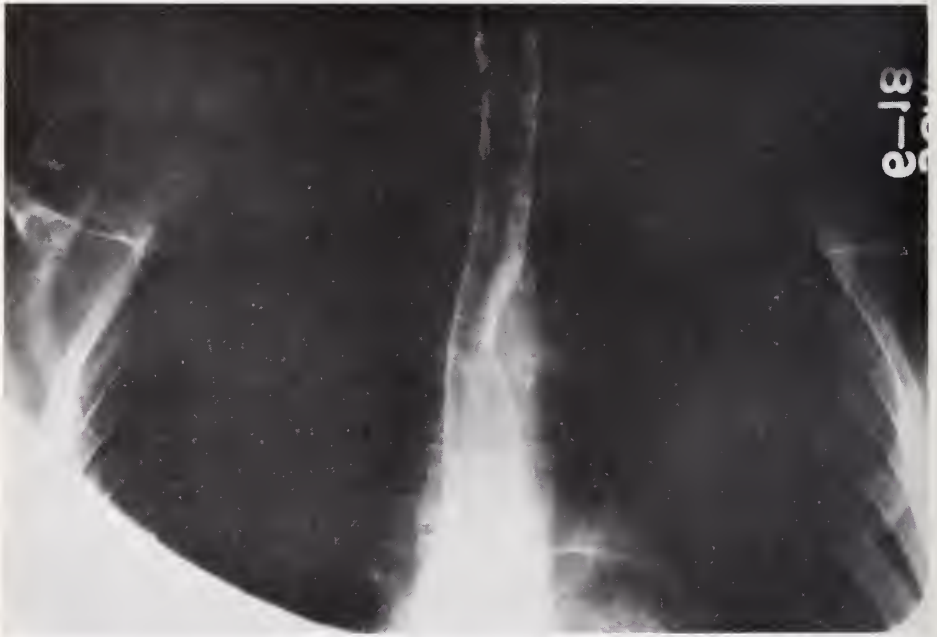


FIG. 2. Flat impression on the left lateral wall of the esophagus a short distance below the thoracic inlet.

had been identified on the posterior aspect of the thyroid gland but only three were removed. This would signify the presence of a fifth gland.) Post-operatively the patient experienced tingling of the extremities and a Chvostek sign could be elicited. In view of her symptoms, and in spite of serum calcium levels consistently in the range of 9.0 mg%, she was placed on vitamin D 50,000 units twice daily and calcium lactate.

Over the next three years, the patient was followed in the Endocrine Clinic. Multiple serum calcium determinations were within the normal range. On October 2, 1962, the patient presented with nausea, headache, vomiting, polyuria of two months' duration and was admitted to the hospital. The serum calcium was 13.0 mg%. The vitamin D and calcium lactate were stopped while a high fluid intake was encountered. The blood urea nitrogen was

25 mg%. The serum calcium returned to normal levels and all the patient's symptoms were relieved.

The patient has now been followed for over one year while off all therapy and has continued to have a serum calcium level in the range of 9-10 mg%. She has experienced no tetany or tingling of the extremities but a Chvostek sign can still be elicited.

DISCUSSION

The involvement of several endocrine glands is the characteristic feature of multiple endocrine adenomatosis. The entire symptom complex need not be manifested when the patient initially seeks medical attention. Our patient developed amenorrhea at the age of thirteen secondary to a pituitary adenoma; renal stones at the age of twenty-four; and episodes of hypoglycemia at the age of twenty-nine, consistent with previous reports that the symptoms may successively appear at long intervals, thus making early diagnosis of the complete syndrome difficult and dependent upon periodic complete endocrine evaluation.

Once the diagnosis of multiple endocrine adenomatosis has been established, investigation of the patient's entire family is indicated. Pedigree studies have demonstrated transmission in an autosomal dominant fashion with a high degree of penetrance (10). Evidence also indicates that this syndrome may arise *de novo*, probably as an autosomal mutation.

Symptoms of hypoparathyroidism occurred in our patient following removal of a fourth parathyroid gland (an ectopic parathyroid adenoma demonstrated in the superior mediastinum by barium swallow). Although hypocalcemia never developed she was treated with vitamin D and calcium until she subsequently manifested hypercalcemia with nausea, vomiting, polyuria, polydipsia and headache. After cessation of therapy, the serum calcium returned to normal levels and has continued so, indicating the presence of a remaining functioning parathyroid gland which in retrospect had been demonstrated at the first parathyroid operation and left in place. A point not frequently emphasized is that approximately 33 per cent of the population has more than four parathyroid glands (11). Since symptoms of hypoparathyroidism after removal of a parathyroid adenoma can be the result of a rapid fall in serum calcium associated with hyporesponsiveness of the remaining, previously suppressed, parathyroid tissue, and avidity of the osteoporotic bony matrix for calcium, it follows that gradually decreasing supplemental therapy over a prolonged period of time may be required to determine whether lifetime treatment is needed (12).

The standard glucose tolerance test is of little value in establishing the diagnosis of organic hypoglycemia, since there is no particular pattern in patients with insulin secreting tumors (13). The patient under discussion demonstrated a diabetic curve on two occasions. The tumor, probably secreting a constant amount of insulin, suppresses the normal islet tissue so that there is little if any response to the glucose load, resulting in a typical diabetic

curve. More prolonged fasting or prolongation of the glucose tolerance test results in hypoglycemia. The unresponsiveness of the normal islet cells may be overcome by placing the patient on a high carbohydrate diet for several days prior to performing the glucose tolerance test.

SUMMARY

A patient is presented with multiple endocrine adenomatosis followed for ten years (age 30-40), with involvement of the parathyroid, pituitary, pancreas, thyroid and adrenal glands. Secondary amenorrhea due to a presumed chromophobe adenoma of the pituitary occurred at the age of thirteen and succeeding symptoms of parathyroid and islet cell hyperfunction occurred eleven and sixteen years later. Pituitary irradiation arrested the headaches and bitemporal hemianopsia but secondary hypogonadism was permanent. Subtotal pancreatectomy with removal of two functioning islet cell adenomata relieved the hypoglycemic episodes. Four histologically identified parathyroid glands (three adenomata, including an ectopic mediastinal adenoma demonstrated by barium swallow) were removed. Since hypocalcemia did not develop, a fifth functioning parathyroid gland is still present, stimulating a brief pertinent discussion of the management of postoperative hypoparathyroidism.

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A Clinical Study of Myeloradiculopathies Associated with Diabetes Mellitus

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In the presence of diabetes mellitus, a tendency exists to relate causally the neurological symptomatology and findings to this disease, *e.g.*, diabetic neuropathy, myelopathy due to diabetes, diabetic encephalopathy. Neurological syndromes have been considered "frequently diffuse and disseminated and may present a bizarre picture" (1). The most common neurological picture is a diffuse polyneuropathy, usually of the lower extremities. An asymmetric, predominantly motor neuropathy or radiculopathy has also been described (2). One group of unselected known diabetic patients studied clinically and by electromyography showed alterations in peripheral nerves with or without overt neurological signs and symptoms (3). Ellenberg proposes that neuropathy is one of the five cardinal features of the diabetic disorder (4). However, he has not only stressed the neurological manifestations in diabetes mellitus, but he has also written of "pitfalls in diagnosis" wherein a neurological syndrome was reputed to be due to a diabetic etiology but was later discovered to be caused by another etiological agent (1).

The question has been raised as to whether the relationship between neurological syndromes and diabetes mellitus is coincidental rather than causal. In an attempt to clarify this problem, this paper reports on an unselected group of patients with spinal cord, spinal root, and nerve disease admitted to this institution over a one-year period of time. Significantly, there was only one case of "polyneuropathy due to diabetes mellitus." This reflects the admitting policy of physicians at this institution and not the incidence of this particular syndrome. The neurological and diabetic out-patient clinics have many patients with this manifestation.

MATERIAL

Two hundred hospitalized patients were studied on the Neurological Service because of disease referable to the spinal cord, roots, and/or nerves (Table I). The incidence of diabetes mellitus in this group was 25 per cent (51 cases).

The nine known diabetic patients initially had symptoms such as polydipsia, polyuria, weight loss, multiple furuncles, and a fasting blood sugar determination confirmed the clinical impression. The other 41 cases were diagnosed after being given 100 Gm glucose orally (in the morning—breakfast was withheld) and two hours thereafter blood was drawn for analysis. In

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TABLE 1
Myeloradiculopathies

	Clinical Diabetes	Positive 2 Hr Glucose Tolerance Test	Negative 2 Hr Glucose Tolerance Test	Glucose Tolerance Test Not Done	Total
Group I. (73 patients)					
A. Neoplasm					26
1. Benign	6	0	5	2	
2. Malignant	0	5	7	7	
B. Amyotrophic lateral sclerosis	0	0	4	5	9
C. Pain syndromes	0	0	8		8
D. Infection	1	0	5	2	8
E. Multiple sclerosis	0	0	2	4	6
F. Trauma	0	0	4		4
G. Congenital	0	0	2	2	4
H. Vascular	0	1	0	2	3
I. "Myopathy"	0	0	2	1	3
J. Radiation	0	0	1		1
K. "Diabetic peripheral neuropathy"	1	0	0		1
Group II. Mechanical obstruction (68 patients)					
A. Kyphoscoliosis	0	0	0	1	1
B. Herniated cervical disc	0	0	1		1
C. Cervical spondylosis					37
1. Myeloradiculopathy	2	8	10	3	
2. Radiculopathy	0	3	4	1	
3. Myelopathy	0	1	2	3	
D. Lumbosacral herniated discs					29
1. L2-3	0	0	0	1	
2. L4-5	0	1	4	6	
3. L5-S1	0	3	1	5	
4. Multiple	1	1	3	3	
Group III. Undiagnosed (59 patients)					
A. Cervical region					34
1. Myeloradiculopathy	0	4	3	3	
2. Radiculopathy	0	2	2	6	
3. Myelopathy	3	4	3	4	
B. Dorsal-lumbosacral region					25
1. Myeloradiculopathy	1	3	3	2	
2. Radiculopathy	0	3	3	1	
3. Myelopathy	0	3	5	1	
Total	9	42	84	65	200

almost all these cases this two-hour glucose tolerance test was repeated when an abnormal blood sugar was discovered. Since 65 patients had only fasting blood sugar determinations, the percentage may have even been higher. Nevertheless, 25 per cent is much greater than the general incidence of diabetes mellitus in the population and, superficially, seems to imply that the metabolic disorder is more than a coincidental factor with respect to neurological disease of the spinal cord, roots, and nerves.

A more detailed look at these patients reveals interesting data. The patients have been divided into three groups.

GROUP I

Group I consists of those whose diagnosis was established and usually suspected upon admission. This may explain the relatively high (25 of 73) incidence of patients who did not have blood sugar determinations two hours after an oral dose of 100 Gm glucose. Except for the diabetic patient with peripheral neuropathy and the patient with an epidural abscess, diabetes mellitus seemed incidental and of no significance.

A. Of the benign spinal cord tumors, one had a granuloma, one a meningioma, and five had neurofibromas (three of these five suffered from generalized neurofibromatosis). The two patients who did not have generalized neurofibromata were both in the seventh decade of life and were thought to have cervical spondylosis. Myelography revealed the neoplasms. Also noteworthy was the fact that one of the patients with neurofibromatosis was studied in 1949 because of cervical radicular pain. Myelography revealed multiple partial blocks due to neurofibromata, but she was not operated upon until 1961 when she developed a paraparesis and evidence of compression of the spinal cord at T-7.

Of the malignant tumors, 11 were metastatic (five from the breast, three from the lung, two from the prostate, and one from the stomach). Three of these patients presented primarily as suffering from neurological disease—two with spinal cord lesions (from the breast and from the lung) and one with a Horner syndrome and a thoracic radiculopathy (from the lung). The remaining eight cases had lymphoma (three), multiple myeloma (one), Hodgkin's disease (one), angiosarcoma (two), and primary intramedullary melanoma (one). Terminally, one of the patients with lymphoma had extensive involvement of spinal cord, brain stem and cerebrum. Post mortem examination revealed no infiltration by malignant cells, but a patchy demyelinating process. This type of pathology associated with malignancy is now being recognized more frequently.

B. Of the nine cases of amyotrophic lateral sclerosis, one was a 2 year old girl, two were patients in their late forties, and six were in the sixth and seventh decades of life. The latter group can sometimes be a diagnostic problem, especially when seen before the illness is clinically noted in many parts of the body. When beginning in the upper extremity, the differential diagnosis includes spinal cord tumor and cervical spondylosis (myelography was performed in two such cases). However, with the more recent advances in electromyography, the diffuseness of the pathology can be sometimes substantiated without resorting to myelography.

C. The pain syndromes were present in eight patients who complained of pain, usually radicular in type, but who did not have any objective neurological findings. Four of these were thought to be suffering from severe psychiatric disturbances. However, their pain was so intense that they were

hospitalized to rule out positively any organic basis to these complaints. One of them (a nurse) had a myelogram, because she insisted that she had a lesion and wanted absolute proof that there was none. The remaining four patients had acute pain syndromes for a matter of weeks—one following an accident in which a chipped fracture of the second cervical vertebrae was noted. Myelography in all these patients revealed no changes which could explain the symptoms.

D. In the infectious cases, one patient, who had diabetes mellitus, developed an epidural abscess of the thoracic region; five patients had diffuse progressive polyradiculopathy, in which the cerebrospinal fluid protein increased in time and no cells were noted (Guillain-Barré syndrome); two patients had spinal cord changes secondary to bone disease, due to tuberculosis and due to non-specific osteomyelitis with a history of subacute bacterial endocarditis.

E. The patients suffering from multiple sclerosis are an important group. They were relatively young (in the third and fourth decades of life). Their disease manifested itself only as spinal cord dysfunction. All had complete normal myelograms. They were considered as suffering from multiple sclerosis only because they had repeated attacks of spinal cord disease. One of this group of patients subsequently developed evidence of a lesion in another site of the central nervous system. Actually, without a history of remissions and exacerbations, a patient would be considered as suffering from myelopathy of undetermined origin. This underscores the thought that the diagnosis of multiple sclerosis is reserved for those patients usually in the younger age group who have multiple attacks of central nervous system disease in time, with multiple sites involved. If only spinal cord dysfunction occurs, myelography is almost mandatory. It is well known that spinal cord tumors, especially in the high cervical cord (foramen magnum region) can produce a syndrome of multiple attacks (with progression) of spinal cord disease.

F. The small number of patients with traumatic disease is due to the fact that most accident cases go to the emergency rooms of the municipal hospitals, rather than to this institution. Actually, only two cases were accidents. One of the other patients had thoracic radicular pains and a history of "black-outs," which when described suggested grand mal convulsions. This patient had multiple compression fractures from T-6 to T-12 vertebral bodies. Whether they were causally related to the grand mal seizure is dubious. The incidence of grand mal seizures is quite high and compression fractures to this extent are relatively rare (such cases usually involve one or two vertebral bodies). The fourth patient injured her right upper extremity at work and developed a causalgia. There was a strong psychogenic component to her illness. It is noteworthy that she had seven stellate ganglion blocks and, finally, a right dorsal sympathectomy.

G. The congenital cases consisted of one Arnold-Chiari malformation, which presented as the picture of an intramedullary cervical cord tumor, two cases of spondylolithesis with a sciatic syndrome, and one patient with subarachnoid sacral cysts. However, the latter entity is not an uncommon incidental

radiological finding and one wonders whether it is of any etiological significance.

H. There were three patients with known intrinsic vascular disease, one with lupus erythematosus and two with periarteritis nodosa. This does not reflect the incidence of neurological involvement due to collagen disease, which is relatively high. Apparently, neurologists are not asked to see such cases unless they are of exceptional significance. The patient who had lupus erythematosus had seizures apparently of spinal cord origin and has been reported in detail (5).

I. The three cases of myopathy are interesting insofar as two of them were relatively early cases and myelopathy was also considered. In one, the cerebrospinal fluid protein was abnormally high and there was a partial manometric block with the head in flexion. Myelography was normal. Biopsy confirmed the diagnosis of myopathy. The other patient complained of back pains and had a proximal type of muscle weakness with hyperreflexia and a right Babinski sign; myelogram was normal. The third case was interesting because she developed a myopathy while on steroids for rheumatoid arthritis. Electromyography revealed abnormal potentials with evidence of lower motor neuron disease, but the muscle biopsy revealed a myogenic type of pathology.

J. The patient with radiation myelitis had a carcinoma of the tongue. He had a hemisection of the tongue and a radical neck dissection, followed two years later with radiotherapy. Twenty-four months thereafter, he developed a paraparesis, with a Brown-Séquard syndrome at C-4. A myelogram was performed because of the possibility of metastatic carcinoma. Cervical spondylosis was noted instead and thought to be the cause of his spinal cord disease. However, he then developed pneumonia and died. Post mortem examination then revealed changes seen in radiation myelopathy—not spondylosis.

K. The patient with peripheral neuropathy was 26 years of age and had diabetes mellitus since 14 years of age. This illness was present also in his maternal grandmother and his paternal grandfather. He had had pin and needle sensations in the distal parts of all four extremities for two to three years. For one and a half years, he had had difficulty in maintaining an erection and also noted "poor ejaculation." Nocturnal diarrhea had been present for three to four months prior to a hospital admission precipitated when he fell asleep with a heating pad applied to his leg for a bruise, and awoke with third degree burns of the extremity. Neurological examination revealed hyporeflexia, and a glove-and-stockings type of sensory defect to pin, touch, and temperature. Vibration and position sense were normal. The presence of only one case of peripheral neuropathy in this series seems to be due to the fact that, in our institution, such patients are treated on an out-patient basis rather than hospitalized. Although there seems to be a high incidence of peripheral neuropathy in patients suffering from diabetes mellitus, there is disagreement as to whether the condition represents a metabolic

disturbance per se of the peripheral nerves (6), or whether the pathology is secondary to a vascular disease, which in turn is influenced by the diabetes mellitus (7).

GROUP II

Group II consists of sixty-eight cases in which mechanical obstruction seemed related to the clinical syndrome. Kyphoscoliosis and a herniated cervical disc seemed definite, as were six cases of myeloradiculopathy due to cervical spondylosis, in which complete or partial manometric blocks existed. Interestingly, there were six additional patients who had diabetes mellitus as well as cervical spondylosis with evidence of block of cerebrospinal fluid flow. Of these, five had no knowledge of diabetes mellitus, but the two-hour blood sugar determinations after 100 Gm oral glucose were abnormally high. The sixth patient was a 63 year old man, who suffered from diabetes mellitus for fifteen years. For twelve months he had had difficulty in urination, with frequency and dribbling and occasional urinary incontinence. He had become constipated during the four months prior to admission. He also admitted difficulty in having and maintaining an erection for at least twelve years. For ten years, he had had pin and needle sensations in the hands and occasionally in the feet—occurring daily—usually in the morning and relieved by “shaking” the extremities. The neurological examination revealed a paraparesis of the lower extremities, hypoactive deep tendon reflexes, but absent ankle reflexes. Vibration sense was impaired in the feet; there was a defect to touch below the knees; position sense errors were noted in the right foot; there was a hypoalgesia from L-3 to S-4 in the left lower extremity. A myelogram revealed marked ridging of C3-4, C4-5, C5-6, and C6-7. An intravenous pyelogram revealed dilatation of the upper urinary tracts and an overdistended urinary bladder. A cystometrogram could not substantiate hypotonicity. He had an enlarged prostate, which was relieved by surgery. This case is important because, as Ellenberg has cautioned, a case for myelopathy due to diabetes mellitus could have been made prior to myelography and urological examination (1). Actually, a similar case with bladder and sexual difficulties exists among the six cases of nondiabetic patients with cervical spondylosis and a manometric block.

In the experience of the Neurological Service, the question of the significance of dysfunction of sexual performance has been most difficult to evaluate. The question, a deeply personal one, doubtfully can be candidly dealt with when one sees a patient for the first time on a consultative basis. Also, the symptom is not uncommon after the fourth decade of life. Whether this represents aging, psychogenic problems, neurological defects with or without diabetes, cannot be easily determined. Even when a 26 year old patient with diabetes mellitus since the age of 14 has admitted difficulty in sexual performance, one may raise the question as to how his metabolic disease has affected his ego development. Nothing is known of his “intrapsychic dynamics” and

how much the illness, beginning in puberty, may have psychologically traumatized him.

The remaining cases diagnosed as cervical spondylosis had patterns of disease—myeloradiculopathy (eleven), myelopathy (six), radiculopathy (eight)—which were similar with or without the presence of diabetes mellitus. In this group of patients with mechanical obstructions, of the 14 “diabetic” patients, all except the patient described above had no knowledge of the fact that they suffered from this illness. The diagnosis was made because of an abnormal blood sugar obtained two hours after the oral administration of 100 Gm of glucose. Actually, in these cases, some neurologists have even challenged the causal relationship between the bony defects and the clinical syndrome. This is due to the relatively high frequency of “incidental” bony defects during myelography. For example, a patient may have cervical symptoms without symptoms of lumbosacral disease, but have significant lumbosacral myelographic defects, as well as an abnormal cervical myelogram. Conversely, patients with abnormal lumbosacral findings and symptoms have had incidental myelography of the cervical region, which has revealed defects in the latter region without any clinical symptoms or findings.

The 27 cases of lumbosacral herniated disc revealed similar problems. Only six patients were diabetic. However, myelographic evidence of disc herniation altered the diagnosis. Ellenberg has detailed two such cases in his paper on “pitfalls in diagnosis.” The fact that only fasting blood sugars were studied in 14 of 27 cases seems to indicate some prejudgment as to the etiology. Most of these cases were seen by an orthopedist prior to neurologic consultation. Five of the six diabetic patients did not know of this condition, but the two-hour blood sugar determinations after 100 Gm of oral glucose revealed abnormalities. The 64 year old patient with known diabetes mellitus had been treated for two years with Orinase. He had a three-week history of severe pain beginning spontaneously in the left buttock and radiating down the posterior lateral aspect of that extremity into the foot. There were no other current neurological symptoms other than constipation “for years.” However, he had had prostate surgery a few years previously and he admitted to having no sexual relations over the past three years. The neurological examination revealed a normal mental status and cranial nerves, weakness of the left lower extremity, proximal function being equally as involved as distal function, atrophy of the left calf, fasciculations in both legs, equal and active deep tendon reflexes. No Babinski sign was noted. There was a hypoalgesia bilaterally below T-5, with vibration sensibility impaired bilaterally up to T-3. Position sense errors were made in the toes of both feet. Laboratory tests revealed a fasting blood sugar of 168 mg% and a two-hour blood sugar was 250 mg%. Standard x-rays were abnormal, with marked changes of the lumbosacral vertebrae and of the midcervical vertebrae, especially at C-4 and C-5. Myelography demonstrated a narrow lumbosacral spinal canal, with multiple indentations at L2-3, L3-4, L4-5, L5-S1, as well as multiple anterior ridges with obliteration of the root pouches at C3-4, C4-5,

C5-6, C6-7, and C7-T1. The diagnosis rested between diabetic myeloradiculopathy, cervical spondylosis, and multiple herniated discs—or all three. He was listed in the category of herniated discs because of the symptom of three weeks of sciatic pain.

In some cases, it would seem that determination of a causal relationship depends more on a physician's orientation than on objective evidence. The orthopedist notes a clinical syndrome with involvement of the spinal cord and roots, and if there are significant bony defects on standard x-rays corroborated by myelography, the patient has spondylosis, or herniated discs. This, for example, would explain the relatively infrequent two-hour post-100 Gm oral glucose blood sugar determinations in patients initially seen by bone specialists.

On the contrary, physicians specializing in diabetes mellitus are convinced that the results of the two-hour tests are significant and when abnormal indicate that the patient suffers from diabetes. When the patient simultaneously has neurological disease and the cerebrospinal fluid protein is abnormally high, a causal relationship is frequently assumed. However, it should be stressed that the relationship may be coincidental and that, alternatively, there is a possibility of mechanical obstruction. Thus, an abnormally elevated cerebrospinal fluid protein is not diagnostic of diabetic involvement of the central nervous system and, indeed, even in patients with diabetes more often seems to correlate with mechanical impingement upon the spinal cord and root.*

In Group II, inasmuch as all these patients had evidence of mechanical obstruction with or without diabetes mellitus, it is not thought necessary to implicate the metabolic disorder.

GROUP III

Group III consists of fifty-nine patients in whom no diagnosis could be determined. Twenty-three of these patients were thought to suffer from diabetes mellitus, only four of whom were known diabetics. The other 19 patients were diagnosed by the two-hour blood sugar determination after 100 Gm oral glucose. It is again to be noted that 17 patients had only fasting blood sugar tests and, of course, there may be additional "diabetic" cases. The pattern of neurological illness was similar whether diabetes mellitus was present or not: that is, myeloradiculopathy, myelopathy, and radiculopathy.

The following clinical summaries detail the neurological manifestations in 14 patients. Except for the abnormal blood sugar determinations among the diabetic patients, the following tests (done as indicated) were found to be normal: blood count, urinalysis, sedimentation rate, blood chemistries, lupus preparation, diagncx blue test, and porphobilinogen. (The latter determination, however, was not done in all cases.)

*See Walter Sencer, *The Cerebrospinal Fluid in Myeloradiculopathies Associated with Diabetes Mellitus*, this issue of the *J. of the Mt. Sinai Hosp.*, p. 202.

Case 1. A 71 year old man was well until eight months prior to admission, when he developed spontaneous pain in the right buttock radiating down the posterolateral aspect of the thigh to the foot. He developed pin and needle sensations in the right calf and, within two weeks, his leg became weak. The pain and the abnormal sensations disappeared, but the weakness remained and progressively began to involve the other extremity. A month prior to admission, he developed pain and weakness in the right shoulder region. He could not raise his hand to comb his hair or to shave. He then noted a rash over the outer aspect of that arm. Within a week, pin and needle sensations occurred in the fingers of both hands.

The general medical examination was normal. The above-noted rash had disappeared.

Neurological Examination: Mental status—There was no organic mental syndrome. Cranial nerves—The cranial nerves were intact. Motor status—There was a marked paraparesis in the lower extremities, evidenced by poor tapping, pivoting and hopping. Abduction and elevation at the right shoulder were poor, and the deltoid muscle was atrophic. There was atrophy of both calves and of the posterior thigh muscles. Fasciculations were noted in all four extremities and in both scapular regions. Reflexes—The biceps and triceps reflexes were absent, the knee and ankle reflexes hypoactive. No Babinski sign was noted. Sensory examination—There was hypoalgesia in the right upper extremity involving the fifth through seventh cervical dermatomes. There was also hypoalgesia in the right lower extremity involving L-4, L-5, and S-1. There were concomitant temperature defects in the same areas. Position sense was normal. Vibration appreciation was diminished in both lower extremities, including the ilia, and in both upper extremities distally to the elbows.

Special Laboratory Tests: The lumbar puncture was normal, except for the cerebrospinal fluid protein (87 mg%); lumbosacral-cervical myelography was normal. Electromyography revealed evidence of denervation of the right deltoid, biceps, brachial radialis, and anterior tibial muscles.

Case 2. A 66 year old woman was hospitalized with a one-year history of low back pain and stiff neck. During the three months prior to admission, she developed stiffness and weakness of both legs, and also the right upper extremity. There were no other neurological symptoms, except that nine years ago, and sporadically since, there were episodes of fecal incontinence. There were no urinary disturbances.

The general medical examination was normal.

Neurological Examination: Mental status—There was no organic mental syndrome. Cranial nerves—The cranial nerves were intact. Motor status—There was a paraparesis with marked weakness of hip flexors. Reflexes—The deep tendon reflexes were equal and active. There was no Babinski sign. Sensory examination—All modalities were normal, except for vibration appreciation, which was impaired in both lower extremities from toes to ilium.

Special Laboratory Tests: The lumbar puncture, and lumbosacral-dorsal-cervical myelography were normal.

Case 3. A 65 year old woman was admitted with a five-year history of progressive weakness of both lower extremities. For four years, she had had difficulty in urination, with frequency and incontinence. Three weeks prior to admission, there developed numbness in the toes of the left foot.

The general medical examination was normal.

Neurological Examination: Mental status—There was no organic mental syndrome. Cranial nerves—The cranial nerves were intact. Motor status—She walked with a broad-based gait and there was a paraparesis of the lower extremities, with weakness most evident proximally. There was weakness of both sternocleidomastoid muscles. Reflexes—The deep tendon reflexes were equal and active. There were bilateral Babinski signs. Sensory examination—She had hypoalgesia with a level at T-1 bilaterally. She made position sense errors in the toes of both feet. Vibration appreciation was impaired bilaterally with a level at T-4.

Special Laboratory Tests: A sweat test revealed no sweating below the umbilicus. Cysto-

metrogram revealed a hypotonic bladder. Lumbar puncture and lumbosacral-dorsal-cervical myelography were normal.

Case 4. A 58 year old man was well until three months prior to admission, when he suddenly had a severe attack of difficulty in breathing. An emergency admission to another hospital revealed him to be in acute congestive heart failure. He then developed urinary retention, which persisted and necessitated prostatectomy (performed under spinal anesthesia). Prior to surgery, the only urological symptom was occasional nocturia during the past ten years. He asserted this occurred when he was awakened during the night by "my old groin pain." This discomfort had been present for thirty years, occurred daily, and had been refractory to various treatments. Twenty-four hours after surgery, he developed numbness in the right foot, involving the first, second, and third toes, and to a lesser degree, the toes of the left foot. Four weeks later, pin and needle sensations ensued in the feet and lower third of both legs. He also noted severe pain in "the bones" of the feet, so severe that he was unable to walk or stand. There was concomitant difficulty in starting the stream of urination, occasional dribbling, but no incontinence.

The general medical examination revealed moderate congestive heart failure.

Neurological Examination: Mental status—There was no organic mental syndrome. Cranial nerves—The cranial nerves were intact. Motor status—He walked with a broad-based gait and could not tandem walk. The Romberg test was negative. Tapping was poorly performed with the left foot. He could not hop on the left leg. The right big toe could not be dorsiflexed and dorsiflexion of the second, third and fourth toes was weak. Hopping was poorly performed with the right lower extremity. Reflexes—The deep tendon reflexes were equal and active, except for the ankle reflexes, which were only present upon reinforcement. No Babinski signs were noted. Sensory examination—There was a hypoalgesia involving the lower third of the right leg and the dorsum of the foot and toes. Temperature sensibility was decreased in the same areas. Position sense errors were made in the toes of both feet. Vibration sense was impaired in both ilia and below. There was a hypesthesia in the toes and dorsum of both feet.

Special Laboratory Tests: The lumbar puncture and a lumbosacral-dorsal myelogram were normal. An electromyogram was normal. Standard x-rays of the cervical spine revealed encroachment of the spinal canal at C5-6. The anterior-posterior diameter was 10.5 mm.

Case 5. A 50 year old woman was admitted with a three-year history of gradual, progressive difficulty in walking. Both legs were equally paretic. For two years, she had difficulty in using her hands, as, for example, in cutting meat and buttoning clothes. During the six months prior to admission, there was dribbling of urine and occasional urinary incontinence. For the past three weeks she felt as if both her hands were held down when she attempted to feed herself. She began to drop utensils and noted marked difficulty in attempting to type. There was occasional "twitching" of both lower extremities. Her legs became stiff and swelling of both legs ensued.

The general medical examination revealed bilateral pitting edema, and there was deformity and atrophy of the right forearm, which had been present since birth.

Neurological Examination: Mental status—There was no organic mental syndrome. Cranial nerves—The cranial nerves were intact. Motor status—The patient could not walk. There was marked spasticity of both lower extremities. There was some movement at the knees but almost total paralysis of the feet. There was distinct weakness of all fingers in extension, abduction, and adduction; wrist extensors were slightly paretic. Power at the elbows and shoulders was normal. There was atrophy of the interossei muscles in both hands. Reflexes—The deep tendon reflexes were equal and active in the upper extremities, the knee reflexes were relatively hyperactive and equal, the ankle reflexes were hypoactive. There were bilateral Babinski signs. Sensory examination—There was a mild hypoalgesia and concomitant defects to temperature sensibility in both lower extremities. There was sacral sparing. Position sense errors were made in the toes and fingers of the four extremities. There was bilateral

stereo-anesthesia. Vibration appreciation was impaired in the fingers of both hands and in both lower extremities at the ilium and below.

Special Laboratory Tests: Lumbar puncture, lumbosacral-dorsal-cervical myelogram and myelencephalogram were normal. Electromyography revealed no abnormalities aside from some decrease in the number of motor units.

Case 6. A 59 year old man was admitted with a four-year history of difficulty in balance. He initially noted awkwardness in going down steps and could not feel the steps with the bottom of his feet. The sensation was "as if walking on cushions." Symptoms progressed to the need for a cane. During the past two years he had urinary symptoms—"urination never felt complete"—and he had occasional episodes of incontinence. The only other neurological symptom was "arthritis," a difficulty in clenching his left hand during the previous five years.

Seventeen years ago, he had attacks of coronary thrombosis and, again, ten years ago. He took nitroglycerin for angina.

The general medical examination was not remarkable. There was a slightly enlarged prostate gland. Blood pressure was 170/120.

Neurological Examination: Mental status—There was no organic mental syndrome. Cranial nerves—The cranial nerves were intact. Motor status—His gait was unsteady and he required a cane. The Romberg test was positive. There was paraparesis with foot tapping defective and bilateral heel to knee ataxia. There was no dysfunction of the upper extremities. Reflexes—The knee and ankle reflexes were hyperactive. There were bilateral Babinski signs. Sensory examination—Vibration appreciation was impaired at the iliac crest, the left more than the right, barely present at the right knee and absent below the knees bilaterally. There was loss of position sense in both feet and toes. Pain, temperature, and touch sensations were normal.

Special Laboratory Tests: The lumbar puncture was normal, except that spinal fluid protein was 74 mg%. A lumbosacral-dorsal-cervical myelogram was normal.

Case 7. A 57 year old man was well until three months prior to admission when he developed a thrombophlebitis of the left leg, which was treated with antibiotics. The following month a renal infection occurred and again antibiotics were given. The week prior to admission he awoke in the middle of the night with severe pain in the left posterior aspect of the neck, followed by pin and needle sensations in both shoulders radiating down the extremities to the elbows. At this time, his temperature was 103.2°. The next day he noted marked weakness at the shoulders and elbows and was hospitalized.

The general medical examination was normal.

Neurological Examination: Mental status—There was no organic mental syndrome. Cranial nerves—The cranial nerves were intact. Motor status—There was a marked paresis in the left upper extremity, especially abduction at the shoulder and extension at the elbow. The right upper extremity was similarly involved, but to a lesser degree. He had concomitant finger to nose ataxia. Reflexes—The triceps reflexes were hypoactive relative to the other deep tendon reflexes, which were equal and active. No Babinski sign was noted. Sensory examination—Sensation was normal to pain, temperature, touch, vibration, and position sensibilities. There was definite spinal tenderness in the lower cervical vertebral region.

Special Laboratory Tests: Lumbar puncture and dorsal-cervical myelogram were normal.

Case 8. A 61 year old man was admitted with a five-month history of slow, progressive pain and weakness of the lower extremities which involved both legs equally. Pain was limited to his heels.

The general medical examination was normal except for fever, which was finally attributed to a urinary infection. He also had an enlarged heart, a grade three apical systolic murmur, and two-plus bilateral ankle edema.

Neurological Examination: Mental status—There was no organic mental syndrome. Cranial nerves—The cranial nerves were intact. Motor status—There was a paraparesis of both

legs. Proximal function was more involved than distal function. Reflexes—The deep tendon reflexes were equal and active, except for the ankle reflexes which were absent bilaterally. No Babinski sign was noted. Sensory examination—Vibration was impaired in both lower extremities from the knees to the toes. Position sense, pain, temperature and touch were normal.

Special Laboratory Tests: Lumbar puncture and complete pantopaque myelography were normal.

Case 9. A 51 year old man slipped on ice, twisted his left ankle, and was found to have a fracture five weeks thereafter. Six weeks after a cast was removed he noticed weakness in that leg. This weakness progressed for two months. There was an additional history of transient paraesthesia of the right foot and ankle, lasting ten to fifteen minutes, occurring sporadically over the past two or three years. He denied any other neurological symptoms, except an episode of double vision seven years previously of "weeks" duration.

The general medical examination was normal.

Neurological Examination: Mental status—There was no organic mental syndrome. Cranial nerves—The cranial nerves were intact, except for evidence of bilateral iridectomies which had been performed for cataracts three years previously. Motor status—There was definite weakness of the right lower extremity, as noted on pivoting, tapping, and hopping. Reflexes—The deep tendon reflexes were equal and active in the upper extremities. The left knee reflex and both ankle reflexes were hypoactive. There was a right Babinski sign. Sensory examination—Vibration appreciation was impaired from the ilium to the toes, the right leg more so than the left. Position sense errors were made in the toes of the right foot and the fifth toe of the left foot. Temperature sensitivity was diminished in the right foot. Pain sensation was normal.

Special Laboratory Tests: Lumbar puncture and complete pantopaque myelography were normal.

Case 10. A 58 year old man was admitted with a one-year history of pin and needle sensations of the right lower extremity occurring in episodic attacks and lasting two to three minutes. He also noted infrequent spontaneous "shaking" of the right foot. He had become constipated over the past six months, noted urinary frequency, and two weeks prior to admission an episode of urinary incontinence occurred. Concomitantly, he felt "deadness" of the right foot.

The general medical examination was normal.

Neurological Examination: Mental status—There was no evidence of an organic mental syndrome. Cranial nerves—The cranial nerves were intact. Motor status—There was a paraparesis of the lower extremities, the right leg being more involved than the left. Proximal function was worse than distal function. He could not sit up from a supine position. Reflexes—The deep tendon reflexes were equal and active, except that the left ankle reflex was absent. There were bilateral Babinski signs. Sensory examination—Vibration sensation was impaired in the right leg, from toes to ilium, and in the left foot. Position sense errors were made in the toes of both feet. There was a level to pain sensibility on the right side at T-8.

Special Laboratory Tests: The lumbar puncture and complete pantopaque myelography were normal.

Case 11. A 50 year old man was admitted with a two-year history of slow, progressive weakness of both legs. During this time he admitted to having "poor erection," and did not have sexual intercourse. In the past year there were two episodes of urinary retention requiring catheterization.

The general medical examination was normal.

Neurological Examination: Mental status—There was no organic mental syndrome. Cranial nerves—The cranial nerves were intact. Motor status—There was a paraparesis of the lower extremities. Proximal function was more involved than distal function. No atrophy or fasciculations were noted. Tone was normal. Reflexes—The deep tendon reflexes were hyperactive and equal. There was a transient ankle clonus in the left foot. A Babinski sign was

noted on the left. Sensory examination—The sensory examination was normal to vibration, position, pain, temperature and touch.

Special Laboratory Tests: Lumbar puncture, complete pantopaque myelography, and pneumoencephalography were normal.

Case 12. A 47 year old woman was admitted because of "strange sensations" in both legs and difficulty in walking. Two weeks prior to admission, she noted sudden knife-like pains in her left leg radiating into the big toe. Some moments later, the pain changed into a "numbness" and then a feeling of pins and needles. This abnormal sensation extended down both lower extremities from the hip. There was concomitant weakness in both legs, the left more than the right.

The general medical examination was normal.

Neurological Examination: Mental status—There was no organic mental syndrome. Cranial nerves—The cranial nerves were intact. Motor status—She walked with a wide-based gait. Tandem walking was poorly performed. There was a paraparesis of the lower extremities, the left being worse than the right. Reflexes—The deep tendon reflexes were equal and active. There was a left Babinski sign. Sensory examination—The sensory examination was normal to all modalities, except for diminution in vibration sense in both ilia and below, more so on the left.

Special Laboratory Tests: Lumbar puncture and complete pantopaque myelography were normal.

Case 13. A 46 year old man was admitted with a one-year history of pain in the left buttock radiating posteriorly down to the ankle and also anteriorly into the left groin. His legs were tired, the left more so than the right. There were transient pin and needle sensations in the left foot. Concomitantly, he had urinary frequency and difficulty in initiating urination. For seven months he admitted to inability to maintain an erection and for four months he suffered from constipation.

The medical history was significant in that he had gout, and peptic ulcer was diagnosed at the age of 22.

The general medical examination was normal.

Neurological Examination: Mental status—There was no organic mental syndrome. Cranial nerves—The cranial nerves were intact. Motor status—There was weakness in the left leg, in hip flexors and extensors, knee flexors, and dorsiflexion of the foot. Reflexes—The deep tendon reflexes were equal and active. No Babinski sign was noted. Sensory examination—Vibration sense was diminished in both ilia and impaired in all the toes. Position sense and touch were normal. There was a hypoalgesia in the entire left lower extremity.

Special Laboratory Tests: The lumbar puncture and complete pantopaque myelography were normal.

Case 14. A 68 year old man was admitted for the second time following a four-month history of progressive "shaking" and "cold" feelings in the legs. Six weeks prior to admission, he developed burning pain in the right hand and the right foot. His hands and feet were always cold and he had trouble buttoning his clothes. He also admitted to constipation and nocturia for the past twelve months. The past history was significant in that three years previously he was hospitalized because of episodes of falling. At that time he complained of two attacks in one month in which he had a feeling of "being pushed," and actually fell to the ground. Both times he could not rise without assistance. He denied any other neurological symptoms.

The general medical examination was normal.

Neurological Examination: (First admission) Mental status—There was no organic mental syndrome. Cranial nerves—The cranial nerves were intact, except for bilateral corneal opacities. There was decreased visual acuity in the right eye. The right pupil was miotic; there was ptosis of the right eyelid. Motor status—He walked with a spastic gait. The Romberg test was negative. Associated movements were intact, but there was increased tone in all extremities.

ties. The left hand grip was weak, and fine tapping and pivoting of both feet were clumsy. Reflexes—The deep tendon reflexes were equal but hyperactive. There were bilateral Babinski signs. Sensory examination—There was no apparent sensory abnormality.

Neurological Examination: (Current admission) Mental status and Cranial nerves—No change from the first examination. Motor status—He walked with a shuffling, rigid gait. There was a quadriparesis and all fine movements were slow. There was atrophy of the intrinsic hand musculature. Reflexes—The deep tendon reflexes were equal but hyperactive. There were bilateral Babinski signs. Sensory examination—Vibration sense was impaired at both ilia and below. Position sense and stereognosis were impaired in the left hand. There was normal perception to touch and pin-prick.

Special Laboratory Tests: (First admission) A lumbar puncture was normal, except for spinal fluid protein of 63 mg%. Pantopaque myelography revealed a transverse defect, presumably due to a bony ridge, between C-3 and C-4 vertebrae. With the head in extension, the pantopaque was blocked in the midcervical region.

Special Laboratory Tests: (Second or current admission) Lumbar puncture revealed a partial block in head extension and the cerebrospinal fluid protein was 208 mg%. Cervical myelencephalogram revealed band defects corresponding to C3-4, C5-6, C6-7 intervertebral disc spaces. In the lateral view, there were anterior defects in the pantopaque column at the levels of C3-4, C5-6, C6-7 interspaces.

It is clear that a careful perusal of the above clinical summaries reveals the impossibility of separating the cases with and without diabetes mellitus. *Actually, the odd-numbered cases had this metabolic disorder.*

Case 1 (diabetic) is complicated by the history of a rash, which may have been a herpetic lesion, and the virus of simplex and zoster are well known to cause myeloradiculopathies.

Case 2 (nondiabetic) is one of the few with fecal incontinence. In this series, except for the patient with diabetic peripheral neuropathy, fecal incontinence did not occur in any diabetic patients. Apparently, bowel symptoms (diarrhea with occasional fecal incontinence) may occur among diabetics, but the clinician should be wary of other causes, as stressed by the case report of Whisnant and Love (8).

Case 3 (diabetic) had urinary incontinence with a dorsal cord lesion. She also had bouts of intestinal obstruction. Clinically, there was no evidence of root and nerve disease (even the ankle reflexes were active). The cerebrospinal fluid was normal. This is contrary to the reported cases of diabetic neuropathy with fecal incontinence.

Case 4 seemed to have a peripheral radicular neuropathy, as well as a myelopathy. He was noted to be nondiabetic and, because of his poor medical state, a cervical myelogram was not performed. In view of the narrow A-P diameter of the cervical canal, cervical spondylosis could very likely have been present as well.

Case 5 is the only patient described above who was known to suffer from diabetes mellitus (24 years) and upon admission was taking 45 units of NPH insulin. Incidentally, she had had two previous myelograms in three years prior to the above admission.

Three other patients known to be diabetics were not described. Two of them did not have myelography. The first was a 54 year old woman who had been hospitalized because the diabetes was uncontrolled. It was also noted

that she had a paraparesis which was of eight months' duration. Due to the presence of diabetes, a causal relationship was presumed probable (in retrospect, one can say that cervical spondylosis is just as likely). The second case was a 54 year old man who had suffered from diabetes mellitus for 21 years and was taking 50 units of protamine zinc insulin daily. He had a progressive hemiparesis over a two-year period. There was concomitant atrophy noted of the right shoulder musculature, and bilateral vibration and position sense impairment in the lower extremities. Pneumoencephalography and angiography were done. No myelogram was performed. The third case was a 40 year old woman who was taking Orinase for the past year and a half because of diabetes mellitus. She developed a sciatic syndrome and after two months was hospitalized. Lumbar puncture and myelography were normal.

Case 6 had myeloradiculopathy with urinary incontinence and an abnormally high cerebrospinal fluid protein. However, he was not diabetic and had no evidence of mechanical obstruction. He typifies the lack of evidence to make any etiological diagnosis. Too often, the presence of diabetes mellitus or mechanical obstruction allows the physician to label the patient—but perhaps incorrectly.

Case 7 had a relatively acute and painful radiculopathy. When a two-hour blood sugar determination was reported as abnormal, and with a recent history of infections, an epidural abscess was suspected. Emergency myelography was performed but nothing was found. The spinal fluid protein was normal. One might diagnose diabetic radiculopathy, but viral inflammatory lesions also occur without the presence of diabetes, and who can state positively the correct diagnosis?

Case 8 had relatively acute myeloradiculopathy. He had vibration impairment in the legs and feet and no ankle reflexes. The lumbar puncture and myelogram were normal. He was not diabetic. This is considered unusual, since a large series of cases have been investigated with respect to deep reflexes and most patients with absent ankle reflexes were found to be diabetic (9).

Case 9 (diabetic) had myeloradiculopathy. The cerebrospinal fluid was normal as was the myelogram. He eventually was studied at two other clinics. In both, the initial diagnosis was "demyelinating disease," although one institution suspected diabetes, especially in view of the early development of cataracts. Neither institution had done the two-hour sugar test, although a glucose tolerance test had been advised.

Cases 10, 11 and 12 are somewhat similar—all had myelopathies. The men (Cases 10 and 11) had sphincteric involvement. Lumbar punctures and myelograms were normal. In Case 11, the two-hour blood sugar test was abnormal. Case 12 had normal blood sugar determinations, but her mother was a known diabetic and it was thought that the patient probably would become diabetic and perhaps the neurologic illness was an early forerunner of the metabolic disorder.

Case 13 seemed to have a lumbosacral radiculopathy with sphincteric in-

volvement. However, the ankle reflexes were active and there was no saddle sensory impairment. Spinal fluid and myelography were normal. The two-hour blood sugar determination was abnormal. Diagnosis: Diabetic radiculopathy? Radiculopathy due to unknown cause and diabetes mellitus?

Case 14 demonstrates how difficult it is to make a correct diagnosis. This patient seemed to have a myelopathy due to cervical spondylosis (a fasting blood sugar was 100 mg%). However, following the neurological investigation, he developed urinary retention and was noted to have an enlarged prostate gland. A transurethral prostatectomy was performed. However, it was not completed because of a hypotensive episode which occurred during anesthesia. The postoperative course was progressively downhill and he died. Post mortem examination was obtained and it was noted that there was marked narrowing of the cervical spinal canal, associated with osteophytes, in the region from C5-6. There were no microscopic abnormalities seen in the central nervous system, with specimens being taken from the right precentral gyrus, right corpus striatum, left dentate nucleus and cerebella folia, mid-medulla, caudal medulla, mid and upper cervical cord, mid and lower cervical cord, lumbar cord, and sacral cord.

Thus, under close scrutiny, Group III like Group II reveals no definite evidence as to the causal relationship of spinal cord and/or root disease and diabetes mellitus. Noteworthy is the omission of peripheral neuropathy. There was only one such case in this particular investigation and no statement can be made about this clinical entity. Interestingly, a recent paper concerning peripheral neuropathy implicated an abnormal spinal fluid protein, both qualitatively and quantitatively (10). The former has not been investigated. However, in these cases, the cerebrospinal fluid protein was not consistently elevated in the patients with diabetes mellitus and this is now under study.

It is true that the percentage of cases suffering from diabetes mellitus (8 known cases and 43 chemically demonstrated cases) is much higher than the incidence of diabetes mellitus in the general population. However, this may merely reflect this particular hospital's population or, more specifically, its neurological patients irrespective of the site of the disease, that is, brain, cord, or root. Garland (11, 12) has reported marked involvement of the spinal cord and roots in twelve cases. All his patients had known, relatively severe diabetes mellitus. Although they were intensively investigated, myelograms were not done. However, they all remitted fairly well (contrary to the experience of patients with cervical spondylosis) and it was thought that their neurologic dysfunction was due to the metabolic disorder. Unfortunately, no such case was seen in this series. On the other hand, perhaps diabetes mellitus in some way makes the nervous system more susceptible to other etiological agents, for example, vascular disease. The problem of vascular disease of the spinal cord and roots is a difficult one, inasmuch as pre-autopsy diagnosis is impossible at the present time. It is hoped that future research, as demonstrated in vascular disease of the cerebrum, may clarify

some relationship between diabetes mellitus and atherosclerosis of the blood vessels supplying the spinal cord and the spinal root.

CONCLUSIONS

1. Two hundred cases of spinal cord and root disease were studied. The most common presumed etiology was mechanical obstruction (68 cases). Fifty-nine patients had no definite etiological diagnosis upon discharge, although localization of disease was relatively clear.

2. No special pattern of complaints and findings could be delineated. The patients predominantly had myelopathy, radiculopathy, or myeloradiculopathy.

3. The incidence of diabetes mellitus, both clinically evident and discovered by oral two-hour glucose tolerance test, was 25 per cent, which is much higher than in the general population.

4. It was not possible to relate casually the neuroanatomic diagnosis to the diabetes mellitus.

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The Cerebrospinal Fluid in Myeloradiculopathies Associated with Diabetes Mellitus

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Alpers, in 1925, investigated 19 diabetic patients with neurological involvement and described a slight cerebrospinal fluid protein elevation in nine cases (1). Since then, Joslin and Root reported a series of patients with diabetic neuropathy in which the cerebrospinal fluid protein was normal in 28, abnormal in 72, with values as high as 440 mg% (2). Jordan listed 22 of 40 patients with similar neurological abnormalities in whom the cerebrospinal fluid protein was abnormal (up to 120 mg%) (3). Extensive clinical reports of diabetic neuropathies noted up to 50 per cent of patients with diabetic neuropathies as having abnormal cerebrospinal fluid proteins—usually in the range of 48 to 100 mg%, but occasionally in the range of 200 mg%, 300 mg% and up to 426 mg% (4-8). Madonick and Margolis reported 80 diabetic patients without neurological disease in all of whom the cerebrospinal fluid protein was normal (9). They also listed five diabetic patients (one with a recent hemiplegia and four with peripheral neuropathy) who had abnormal protein values (72, 65, 52, 67 and 210 mg%). Kutt and associates noted abnormal cerebrospinal fluid protein (up to 176 mg%) in 32 of 84 patients with neurological involvement (10). Five of their patients with neurological disease had normal proteins. Two patients without neurological involvement had unexplainable abnormal cerebrospinal fluid proteins. Electrophoretic determinations demonstrated a selective increase of slow alpha 2 globulin in 35 patients, the majority of whom had evidence of vascular and neurological disease, but including four patients primarily with neurological manifestations. An additional patient with neurological disease had the gamma globulin relatively increased.

In a recent review article, Ellenberg states that the most consistent laboratory features of diabetic patients with neurological manifestations is the elevation of the cerebrospinal fluid protein—in his experience in 80 per cent of the cases (11). Contrariwise, he stated it to be normal in diabetic patients without involvement of the central nervous system. The range of protein is usually 60 to 100 mg%, infrequently higher and rarely above 200 mg%.

A recent analysis of a large series of cases with myeloradiculopathy included 51 cases of diabetes mellitus.* This was an unselected group, treated on

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* As used in the current analysis, "peripheral neuropathy" usually refers to a patient with peripheral, bilateral, symmetrical pains and paresthesias of the distal half of the lower extremities, perhaps calf tenderness, decreased to absent knee and ankle reflexes, mild sensory impairment usually to touch, pin, and vibration appreciation. "Radiculopathy" infers root pains with concomitant reflex, sensory, and/or motor impairment. "Spinal cord disease" is usually defined when long tract findings exist, such as hyperreflexia, Babinski signs, sensory levels (including defects in vibration appreciation).

the Neurological Service of this hospital. There was only one patient with "diabetic neuropathy." Most of the patients had spinal cord and/or root disease severe enough to require in-patient care.

Nine patients were known to have diabetes mellitus. Forty-two additional patients were diagnosed when, after 100 Gm of oral glucose, a two-hour blood sugar determination was abnormal (130 mg% or higher).

With respect to spinal fluid manometrics, nine patients with neoplasm and a patient with an epidural abscess had complete blocks. A positive Queckenstedt test in 33 additional patients reflected an incomplete block. 172 patients had pantopaque myelography performed.

MATERIAL

The patients were divided into three groups: I. 69 patients in whom an etiologic diagnosis was apparent, for example, neoplasm, infection, and trauma. II. 67 patients in whom the neurological syndromes seemed due to mechanical impingement upon the spinal cord or roots by bone or herniated nucleus pulposus. III. 56 cases in which no known cause could be definitely established.

Group I (Table I) is noteworthy in that six nondiabetic patients had abnormal proteins for no obvious reason.* Incidentally, of the eight diabetic patients, five had normal cerebrospinal fluid proteins and three had abnormal values. All of the latter had evidence of manometric block.

Group II (Tables II A, II B) is considered separately from Group I because misdiagnosis is a hazard in these cases, as emphasized by Ellenberg (12). As expected, among the nondiabetic patients, 26 had normal and 21 had abnormal cerebrospinal fluid proteins. Of the 20 diabetic patients with spondylosis or herniated disc, eight had normal cerebrospinal fluid proteins. Twelve patients had abnormal values (six of whom had evidence of manometric block).

Group III is important because there has been a recent tendency to label diabetes as the cause of the neurological syndrome when no other etiology can be found, especially when the cerebrospinal fluid protein is abnormal. Of the 33 nondiabetics, seven had abnormal cerebrospinal fluid proteins (one of whom had had a previous myelogram and one did not have a glucose tolerance test). Of the 23 diabetics, 15 had normal cerebrospinal fluid proteins. Eight patients had abnormal cerebrospinal fluid proteins (131, 84, 95, 70, 82, 55, 53, 128 mg%) including two who had had previous myelography and two others who did not have contrast study.

To summarize (Table IV), 28 (four known and 24 "chemical") diabetic patients had normal cerebrospinal fluid proteins. Twenty-three (five known and 18 "chemical") diabetic patients had abnormal cerebrospinal fluid pro-

* Cerebrospinal fluid protein was determined by the sulphosalicylic acid turbidity method, using a Klett-Sumerson photoelectric colorimeter. Although the manufacturer claims that normal values for this instrument range between 20-40 mg%, this has never been tested at this hospital. On the basis of the experience of the Neurological Service, the normal high value has been considered 50 mg% for this study.

TABLE I
Group I. Myeloradiculopathies—Known Etiology—69 Patients

Diagnosis	Age	Blood Sugar*	Queckenstedt Test	Cerebrospinal Fluid Protein (mg%)
A. Tumors				
1. Benign mass				
Granuloma L5	12	64*	+C	clotted
Meningioma D5	72	100	+	68
Neurofibroma C6	75	110	0	211
Neurofibroma C2	43	96	+	55
Neurofibroma D4	52	90*	+C	450
Neurofibroma T12	35	93	+C	535
Neurofibroma D8	19	78*	0	104
2. Malignant neoplasm				
Breast metastases	64	100	+C	330
	62	130, 136	+C	31
	59	132	0	29
	50	74	0	97
	58	114	0	99
Lung metastases	76	186	+C	765
	69	117	+	1300
	69	100	+C	307
Prostate metastases	59	54*	0	12, 16
Stomach metastases	54	100	+C	286
Lymphoma	52	98*	+	1740
	80	124	0	33
	69	72	0	62
Myeloma	28	72*	0	16
Hodgkin	55	58*	0	62
	58	165	+C	72
Angiosarcoma	49	98*	+	82
B. Amyotrophic lateral sclerosis				
	59	106	0	64‡
	68	74	0	28‡
	42	114	0	37‡
	66	67*	0	26
	2	60*	0	20‡
	69	71*	0	
	61	80	0	40, 39
	47	67*	0	39‡
	71	90*	0	57
C. Pain syndromes				
	53	61*	0	34
	38	110	0	43
	46	84	0	20‡
	43	70*	0	80‡
	48	98	0	20, 35
	59	62	0	48, 47
	60	78*	0	32
	53	76*	0	46‡

TABLE I—*Continued*

Diagnosis	Age	Blood Sugar*	Queckenstedt Test	Cerebrospinal Fluid Protein (mg%)
D. Infection				
Epidural abscess, "Guillain-Barré" syndrome	43	378	+ C	pus
	57	160	0	33‡, 120
	59	100	0	56‡, 106, 130
	21	63	0	835‡, 560, 350, 675, 288
	15	76*	0	135‡
"Viral" polyneuropathy	42	62	0	90‡, 92
Pott's disease	48	102	+	238
Osteomyelitis	46	86*	0	35
E. Multiple sclerosis				
	36	70	0	41, 64
	41	114	0	33‡, 36
	41	68*	0	45
	49	88*	0	58
	38	74*	0	51
	48	80*	0	29‡
F. Trauma				
	14	53*	+	123
	43	68*	+	62
	35	66*	0	62
G. Congenital disease				
	43	90*	+	47
	63	93	0	83, 110
		77	0	123‡
	66	70*	0	21, 24
	71	108	0	32
H. Vasculitis				
	45	100	0	468‡
	53	224	0	47‡
I. "Myopathy"				
	60	—*	0	22
	20	96	+	65, 102, 131
	49	90	0	37‡
J. Radiation myelopathy				
	64	126	0	53

* Patients who did not have oral glucose test for diabetes mellitus.

‡ Myelography performed on prior hospitalization.

‡ Myelography not done.

+ Incomplete manometric block.

+C Complete manometric block.

teins; 15 of these patients had disease due to other known causes; two additional patients did not have myelography. Only six of these diabetic patients had no other apparent reason for the abnormally high cerebrospinal fluid protein.

Table V lists the clinically known diabetics, the duration of their diabetes and the lumbar puncture results.

TABLE II A

Patients with Mechanical Impingement upon Spinal Cord or Root—Nondiabetic—47 Cases

Diagnosis	Age	Blood Sugar*	Queckenstedt Test	Cerebrospinal Fluid Protein (mg%)
Kyphoscoliosis	52	76*	0	20
Herniated cervical disc	51	100	0	16, 38
Cervical spondylosis myeloradiculopathy	68	100	+	208, 178
	50	84	+	49, 43
	73	97	+	42, 45
	72	85*	+	111, 75
	49	78	+	51
	70	110	+	49
	62	124	+	27
	72	85*	0	57
	50	78*	?	66
	68	86	0	25
	22	72	0	39
	68	80	0	33, 37
	64	116	0	33
Radiculopathy	42	68*	+	130
	42	128	0	55
	54	88	0	100
	49	74	0	53
	54	107	0	25
Myelopathy	55	70*	0	53
	58	74*	0	38, 27
	61	90*	0	46
	70	121	0	107
	62	—*	0	61
Lumbosacral herniated discs				
L2-3	60	—*	0	87
L4-5	48	123	+	31, 26
	64	94	0	30
	40	76	0	53
	46	103	0	32
	45	62*	0	82, 25
	30 ²	63*	0	70
	58	81*	0	70, 105
	26	—*	0	33
	44	82*	0	54
	31	—*	0	41
L5-S1	56	100	0	24
	53	104	0	28, 78
	56	111	?	43
	73	80*		120, 152
	69	72*	0	43
	74	74*	+	48, 59
Multiple	51	—*	0	39
	17	86*	0	64
	49	68*	0	39
	31	—*	0	118
	31	68*	0	43

* 24 patients who did not have oral glucose tolerance test for diabetes mellitus.

+ Incomplete manometric block.

TABLE II B

Patients with Mechanical Impingement upon Spinal Cord or Root Diabetic—20 Cases

Diagnosis	Age	Blood Sugar*	Queckenstedt Test	Cerebrospinal Fluid Protein (mg%)
Cervical spondylosis	42	214	+	61, 43
	66	214	+	124
	60	139	+	120
	52	238	+	86
	60	136	+	53
	63	15 yrs.	+	90
	52	98	0	38
		295	0	49†, 56†
	83	196	0	20
	73	252	0	34
	61	6 yrs.	0	66
	41	160	0	44
	39	180, 235	0	26
	58	214	0	40
	72	162	0	131
Lumbosacral herniated discs	69	146	0	100
	48	137	0	71
	37	204	0	78
	37	180	0	131
	53	160	0	30, 33
	64	2 yrs.	0	43, 52

* Blood sugar values not available. Time refers to duration of known diabetes mellitus.

† Re-admission. Myelography performed on prior hospitalization.

+ Incomplete manometric block.

DISCUSSION

On the basis of this study, the cerebrospinal fluid protein does not seem to be necessarily significant per se as indicative of diabetes mellitus. Nevertheless, there are some aspects to the above findings which should be emphasized.

Of these 192 cases, only one patient had "peripheral neuropathy." This particular syndrome is considered the most common neurological entity among diabetics. However, these patients are rarely hospitalized. In almost all reports of large series of cases, the lumbar punctures were done on an out-patient basis. Naturally, almost no myelograms were performed. One wonders whether some of the abnormal proteins may have been due to coincidental encroachment upon the spinal canal by asymptomatic herniated nucleus pulposus or cervical spondylosis. The one patient in this series with peripheral neuropathy and known diabetes for ten years had a normal cerebrospinal fluid protein and, as in similar cases in the literature, did not have myelography performed.

The question remains as to whether diabetes mellitus has any relationship

TABLE III A
Myeloradiculopathy—Cause Unknown—Nondiabetic—33 Cases

Diagnosis	Age	Blood Sugar	Queckenstedt Test	Cerebrospinal Fluid Protein (mg%)
Cervical region				
Myeloradiculopathy				
	54	117	0	30
	62	80	0	55
	66	82	0	22
	36	100	0	37
	41	76	0	43
	48	62	0	40
Radiculopathy				
	38	—*	+	29
	38	88	0	25, 40
	61	90	0	95, 111
	26	69	0	70
	35	78*	0	37, 59
	32	82*	0	45
	23	84*	0	29
	31	88*	0	49
Myelopathy				
	35	88*	+	25
	59	120	0	74†
	30	90	0	41, 23, 25
	33	103	0	20
	61	100	0	37, 23
	54	58*	0	34
	20	72*	0	74
Dorsal-lumbosacral region				
Myeloradiculopathy				
	57	90	0	65
	47	104	0	20
	67	98	0	27, 22
	72	88	0	29
	49	72*	0	49
Radiculopathy				
	42	110	0	72
	50	100	0	37
	56	62*	0	34, 67
	60	80*	0	48
Myelopathy				
	46	100	0	30
	58	102	0	30
	55	66*	0	44

* 12 patients who did not have oral glucose tolerance test for diabetes mellitus.

† Myelography performed on prior hospitalization.

+ Incomplete manometric block.

TABLE III B

Myeloradiculopathy—Cause Unknown—Diabetic—23 Cases

Diagnosis	Age	Blood Sugar*	Queckenstedt Test	Cerebrospinal Fluid Protein (mg%)
Cervical region				
Myeloradiculopathy				
	71	140	0	131, 87
	65	137	0	47
	50	186	0	35
	59	152	0	43
Radiculopathy				
	58	244	0	84, 34
	57	193	0	43
Myelopathy				
	21	256	0	95†
	64	136	0	21
	50	165	0	70
	65	151	0	20
	50	24 yrs.	0	28
	69	20 yrs.	0	45
	54	21 yrs.	0	82, 10‡
Dorsal-lumbosacral region				
Myeloradiculopathy				
	51	168	0	37
	62	156	0	55, 59
	76	178	0	53
	72	abnormal	0	44, 67
Radiculopathy				
	60	220	0	45, 57
	46	170	0	49
	40	340	0	28
Myelopathy				
	50	184	0	33, 30
	49	164	0	28, 56
	55	2½ yrs.	?	128‡

* Blood sugar values not available. Time refers to duration of known diabetes mellitus.

† Myelography performed on prior hospitalization.

‡ Myelography not done.

TABLE IV

Cerebrospinal Fluid Protein—192 Cases

	Normal—108 Cases		Abnormal—84 Cases	
	Nondiabetic	Diabetic	Nondiabetic	Diabetic
Group I	28	5	33	3
Group II	26	8	21	12
Group III	26	15	7	8
	—	—	—	—
Total	80	28	61	23

to myeloradiculopathy, other than mild peripheral neuropathy. Of 28 cases reported in detail in the literature as having myelopathy and/or radiculopathy due to diabetes mellitus, only four had myelograms performed (13-16). Too often, because of the presence of the metabolic disorder (most of these patients were known diabetics), the causal relationship was assumed. Frequently, corroborating evidence was a statement to the effect that the cerebrospinal fluid protein was abnormally high, a thought derived from the extensive reports concerning patients with diabetic peripheral neuropathy.

Nevertheless, diabetic patients have been reported who developed severe involvement of the spinal cord and roots, with predominant motor impairment (17). Garland thinks that the dysfunction is due to the metabolic disorder (18, 19). All of his 12 cases have remitted fairly well under careful manage-

TABLE V
Patients with Pre-existing Diabetes Mellitus—9 Cases

Diagnosis	Age	Duration of Diabetes*	Queckenstedt Test	Cerebrospinal Fluid Protein (mg%)
"Diabetic" peripheral neuropathy	26	10 yrs.	0	26
Epidural abscess	43	8 yrs.	—	pus
Cervical spondylosis	63	15 yrs.	—	90
Cervical spondylosis	61	7 yrs.	0	66
Multiple lumbar discs	64	2 yrs.	0	43, 52
Unknown etiology				
Cervical region—myelopathy	50	24 yrs.	0	28†
	69	20 yrs.	0	45
	54	21 yrs.	0	82, 107‡
Lumbosacral region—myelopathy	55	2½ yrs.	?	128‡

* Blood sugar values not available. Time refers to duration of known diabetes mellitus.

† Myelography performed on prior hospitalization.

‡ Myelography not done.

ment of the diabetes. These patients were intensively studied, but myelography was not performed. Although the possibility exists of superimposed mechanical causes, cases such as cervical spondylosis rarely get completely better (they may stabilize and not progress).

In our cases, analyses of the clinical manifestations of these patients with myeloradiculopathy yielded no evidence to indicate that the metabolic disease produced the neurological involvement (20). In none of the known diabetic cases has clinical remission occurred to date.

CONCLUSIONS

We have studied 192 patients with myeloradiculopathy. Nine were known to have diabetes mellitus and 42 others had abnormally elevated blood sugar levels two hours after 100 Gm of oral glucose. Of these 51 patients, 28 had normal cerebrospinal fluid protein. Twenty-three had abnormally elevated levels, but at least 15 had other obvious causes for the elevated protein found, besides diabetes.

Of the 141 patients without evidence of diabetes, 61 had elevated cerebrospinal fluid protein. In 36, there was obstruction of or impingement upon the spinal canal. In 13, there was no explanation for the abnormal cerebrospinal fluid findings.

Analysis of our data does not support the conclusion that the finding of elevated cerebrospinal fluid protein in a patient with myelogramulopathy should suggest the presence of diabetes. More: even when the complete triad is present (myelogramulopathy, diabetes, elevated cerebrospinal fluid protein) the diabetes does not necessarily underlie the others. Such a patient is perhaps more likely to have mechanical encroachment upon the spinal canal.

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Spiking Acid Hyperphosphatasia, Splenomegaly, and Leukemoid Reaction During a Hemolytic Sick Cell Crisis

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INTRODUCTION

Since erythrocytes are one hundred to two hundred times as rich in acid phosphatase as the serum (1), it was reasonable to suspect that during a brisk bout of hemolysis sufficient enzyme would be released into the serum to be of diagnostic value. Indeed, such a phenomenon has been alluded to previously (2). During the course of our studies on nonprostatic causes of acid hyperphosphatasia, we came to observe a very unusual case during a hemolytic sickle cell crisis. As predicted, this patient did indeed show a striking degree of acid hyperphosphatasia. This feature and several others of this interesting case justify a report in detail.

CASE REPORT

The patient was a 32 year old Negro female who was admitted to the hospital because of aches in her legs and weakness of four days' duration.

She was known to have sickle cell anemia, and had had dozens of crises since early adolescence. The crises tended to be triggered by menstruation. Five days prior to admission her menses began. Four days prior to admission she began to have generalized weakness and aching all over her body but particularly in her legs and in the left upper abdominal quadrant. These symptoms progressed until admission. It was known that the spleen had not been palpable a year previously.

Examination revealed an asthenically built Negro female in moderate distress due to abdominal and leg pains. There was no fever or icterus. The heart and lungs were normal. A very tender firm spleen was palpable six fingerbreadths below the costal margin in the midclavicular line. The liver was not enlarged. The limbs were normal.

Laboratory workup on admission was as follows: Serial urinalyses showed proteinuria, pyuria, and leukocytic cylindruria without hematuria or azotemia. The chest x-ray, blood sugar, electrocardiogram, and liver profile were normal. The hemoglobin was 5.0 Gm% and the hematocrit 18%. Hemoglobin electrophoresis on filter paper, agar gel, and starch gel revealed pure hemoglobin S, while alkali reduction disclosed 3.6–4.1% hemoglobin F. The white blood cell count was 42,400 with a marked shift to the left. There were 4

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normoblasts and 45 erythroblasts per 100 leukocytes. Many erythrocytes showed basophilic stippling. The reticulocyte count was 3.2%. The platelets were increased. The serum total bilirubin was 0.8 mg%.

During the first ten days of her hospitalization, she had paroxysms of splenic and leg pains and low grade fever spikes. During this same time, the white blood cell count climbed to 150,500, and the reticulocyte count to 35.4%. The platelets were consistently increased in the blood smear. The serum acid phenylphosphatase activity (SAPP) spiked back and forth between 2.1–4.9 Gutman-King-Armstrong units, and the serum total bilirubin climbed to 8.0 mg% (Fig. 1). Thereafter, she progressively improved. The hemoglobin rose linearly, the icterus disappeared, the leukemoid reaction subsided, and the curve of serum acid phenylphosphatase activity fell off in a smooth slope. Over the next several months, the spleen gradually receded under the costal margin until it was no longer palpable.

Hemoglobin electrophoresis (filter paper, starch gel, agar gel) was performed on the patient's mother and three of her siblings. All were found to have the S-A pattern.

METHODS

The serum acid phenylphosphatase activity (SAPP) was determined by the Gutman modification of the King-Armstrong technique (3). This method uses for its substrate disodium monophenylphosphate. As indicated previously, for accurate results it is required that the determination be done soon after the blood sample is drawn, that one brand of substrate be used throughout the study, that fresh substrate solution be prepared every few days, and that precautions be taken to avoid *in vitro* hemolysis (4). The upper limit of normal for women, as determined in our laboratory, is 1.6 units (4).

The total, direct, and indirect bilirubin fractions were determined by the method of Malloy and Evelyn (5). The upper limit of normal of the serum total bilirubin is 1.0 mg% with an approximately equal partition between direct and indirect components.

The hematocrit was measured with the Clay-Adams microhematocrit centrifuge.

DISCUSSION

This unusual case has many facets for discussion. Each will be briefly commented upon under the following headings:

1. *The Crisis*

A. Its nature. Four types of sickle cell crises have been described (6–8): thrombotic, aplastic, hemolytic, and hypersequestration. In our patient, the facts of the case are best explained by assuming hemolysis to be the predominant element. The evidence in support of this hypothesis include the fever, the pronounced jaundice, the leukemoid reaction, and the large number

of reticulocytes, normoblasts, and erythroblasts in the peripheral blood. However thrombosis and splenic hypersequestration cannot be excluded as secondary pathogenetic factors.

B. Its cause. The relation of the crises to menstruation is an unusual one. Its mechanism is obscure.

2. Splenomegaly

The splenomegaly is noteworthy partly because of its infrequency in adults, and partly because of its possible role in the pathogenesis of crises. Causa-

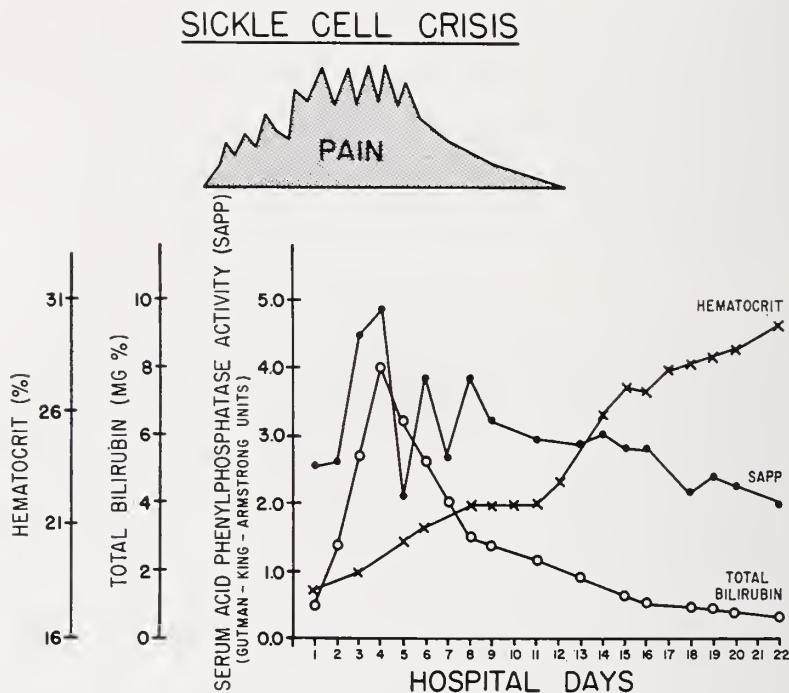


FIG. 1. 32 year old Negro female with acute hemolytic sickle cell crisis.

tive mechanisms for splenic distention have been discussed by Watson (9). A subcapsular hematoma seemed likely in the present case. Congested spleens may cause hypersequestration of erythrocytes, and the resultant stagnation may enhance hemolysis (7, 9, 10). In this way, an enlarged spleen may precipitate a sickle cell crisis.

3. Leukemoid Reaction

The massive leukemoid reaction of 150,500 was a striking feature, and reflected an intense regenerative reaction of the marrow to the hemolytic episode.

4. The Acid Hyperphosphatasia

A. Cause of the acid hyperphenylphosphatasia. It is hypothesized that the acid hyperphenylphosphatasia noted in the hemolytic sickle cell crisis is caused by one or several of the following factors:

1. Erythrocytes are approximately one hundred to two hundred times as rich in acid phosphatase as serum (1), and therefore hemolysis might be expected to raise the serum activity by about this amount.

2. Thrombo-embolic diseases cause acid hyperphenylphosphatasia (4, 11, 12), and the microthromboses so characteristic of sickle cell disease may contribute to the increased SAPP in this way.

3. Platelets are rich in acid phosphatase (13), brisk thrombocytosis is known to follow hemolysis (14), and thrombocytosis is known to cause an increased serum acid phosphatase activity (15). The acid hyperphenylphosphatasia of hemolysis might be at least partially on this basis.

4. Aside from prostate, the tissues richest in acid phosphatase are hematopoietic, liver, spleen, and kidney, though probably all tissues contain the enzyme in some amount (16). During hemolysis, these tissues are injured by anoxemia and might release their contents (including the contained enzymes) into the serum.

B. Cause of the spiking nature of the acid hyperphenylphosphatasia. As a working hypothesis, we suggest one of the following mechanisms as the explanation of the saw-toothed character of the acid hyperphenylphosphatasia:

The muscular aches and pains during the crisis seemed to occur in waves, and it might have been that each paroxysm of hemolysis gave rise to a spike in the SAPP curve. The bilirubin curve would not be expected to reflect these paroxysms, since the time consumed by the metabolic conversion of hemoglobin to bilirubin-glucuronide and the compensatory factor of accelerated biliary excretion tend to smooth out any such irregularities. Similarly, the hematocrit curve would be smoothed out by compensatory replacement of hemolyzed erythrocytes from marrow and storage depots.

Contrariwise, it could be argued that each wave of hemolysis decreases, not increases the SAPP, for red blood cells are very rich in inorganic phosphate (17), and it has been demonstrated (in lower organisms, at least) that excess phosphate suppresses acid phosphatase activity (18). A similar explanation has been given for the fall in SAPP during the terminal phases of uremia (19, 20). The hypothesis that hemolysis transiently raises the serum inorganic phosphate level and thereby inhibits acid phosphatase activity is a tempting one and is presently under study in our laboratory.

C. Sensitivity of the serum acid phenylphosphatase activity is an index of hemolysis. The SAPP appeared to be a sensitive index of hemolysis, regardless of whether one used as the criterion for hemolysis a rise above the accepted upper limits of group normal or a rise above the baseline values for that particular patient (Fig. 1). It is important to note, however, that a high SAPP is a nonspecific finding, for high values may also be observed in a wide variety

of nonprostatic diseases (4, 11, 12, 19, 20–23). Thus the significance of a high SAPP must be judged in the context of its clinical setting. Serial studies are most valuable in this regard and may be crucial.

D. The high baseline serum acid phosphatase. The high baseline SAPP levels in this case probably reflected low-grade chronic hemolysis and/or chronic pyelonephritis (19, 20).

SUMMARY

A study was made of a 32 year old Negro female during a severe hemolytic sickle cell crisis in which the hematocrit fell to about half of its baseline value. A spiking acid hyperphosphatasia up to 4.9 Gutman-King-Armstrong units (normal range = 0.3–1.6 units) was found. The cause of the acid hyperphosphatasia is thought to be release of erythrocyte acid phosphatase into the serum during hemolysis, the microthromboses of sickle cell disease, the thrombocytosis secondary to severe hemolysis, and/or the diffuse tissue injury resulting from the anoxemia of hemolysis. The spiking nature of this acid hyperphosphatasia is felt to be a reflection of the fact that hemolysis itself may occur in paroxysms. Each wave of hemolysis tends to raise the serum acid phosphatase activity by the mechanisms described above, and perhaps also to lower it by releasing erythrocyte inorganic phosphate into the serum. It is conjectured that the resultant of these two opposing tendencies may explain the saw-toothed character of the acid hyperphosphatasia.

Several interesting clinical features of this case are also worth noting. First of all, hemolytic sickle cell crises are said to be rare in adults, and the present case affords a striking example of this unusual phenomenon. Secondly, her many crises seemed to be triggered by menstruation. Thirdly, a massive leukemoid reaction of 150,500 accompanied the hemolytic episode. Lastly, pronounced transient splenomegaly occurred, perhaps because of a huge subcapsular hematoma and/or congestion with hypersequestration.

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A Bleeding Abnormality Associated with Malignant Hypertension

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INTRODUCTION

The occurrence of bleeding as a complication of hypertensive cardiovascular disease is well known. This is generally the result of hemorrhage into various viscera due to arterial wall disease (1). A positive tourniquet test (Rumpel-Leede-Hess) is present in over 50 per cent of patients with hypertension without apparent relation to hemorrhagic episodes (2). Almost all hemorrhage in hypertension is in the cephalic parts of the body—cerebral hemorrhage, retinal hemorrhage, and epistaxis. Hematuria, when present, is most often due to ureteral lithiasis or other complication, but can in rare instances result from arteriolar necrosis in patients in the malignant phase of hypertension (3). However, extensive bleeding into subcutaneous tissues associated with a temporary defect in the coagulation mechanism has not been previously reported in a patient with hypertension who did not have co-existent uremia. The following case report concerns a patient with malignant hypertension and widespread bleeding associated with a prolonged bleeding time in whom hemorrhagic phenomena disappeared with control of his hypertension.

CASE REPORT

J.F., a 40 year old white male, was admitted to the South Nassau Communities Hospital on May 31, 1961, with blurring of vision of five days' duration. For fifteen years the patient noted frequent generalized dull headaches. He had had an elevated blood pressure but had never received any antihypertensive therapy. In 1956 the patient underwent cholecystectomy for cholelithiasis without any bleeding difficulty. Five weeks prior to admission he noted the onset of gross hematuria and easy bruisability. Five days before entering the hospital he noted the sudden onset of blurring of vision. He had received no medication other than aspirin and codeine for his headache during the year prior to this admission.

Family history was significant in that his father had died of a heart attack, his mother had died of a cerebrovascular accident, a sister had died of a cerebral hemorrhage, and his sole living brother was known to be hypertensive.

Physical examination revealed a well-developed, well-nourished stuporous

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male: temperature was 37°C., pulse rate 72 per minute, blood pressure 248/142 in both arms, and 250/144 in both legs, respiratory rate 16 per minute. The pupils were round and equal. The optic fundi showed narrowing and tortuosity of the arterioles, arteriovenous nicking, extensive hemorrhages and exudates and a 1.5 D. papilledema. The patient could barely discern fingers on confrontation. The heart was enlarged 2 cm to the left of the midclavicular line to percussion. Scattered ecchymoses were noted over the lower extremities, and there was no edema. Muscle strength, sensation, and deep tendon reflexes were normal, and no pathological reflexes were noted.

The urine was acid, with 3 plus proteinuria. Sediment contained numerous red cells and occasional white cells per high-powered field. The hemoglobin was 11.0 Gm%, hematocrit 31%, red cell count 3,700,000 cells/cu cm, white

TABLE I

A List of the Coagulation Studies on Patient J.F.

	Patient	Normal
Bleeding time		
Ivy method	24 min.	2-6 min.
Duke method	30 min.	1-3 min.
Tourniquet test		
Rumpel-Leede-Hess	++++	negative
Coagulation time		
Lee-White method	7 min.	5-10 min.
Clot retraction		
at end of 1 hour	normal	—
at end of 24 hours	normal	—
Recalcification time		
Lee-White method	2 min., 28 sec.	2-8 min.
Prothrombin time	15 sec.	15 sec.

cell count 9,600 cells/cu cm, with a normal differential pattern, and the platelet count was 173,000/cu cm. The blood urea nitrogen was 19 mg%, and the non-protein nitrogen 44 mg%, and the creatinine 1.48 mg%. Serum potassium was 3.6 mEq/L, and carbon dioxide 30.6 mm L. The fasting blood sugar and glucose tolerance test, the serum calcium, phosphorus and uric acid were all normal.

The bleeding time was twenty-four minutes (Ivy method (4)) and thirty minutes (Duke method (5)) and a tourniquet test (Rumpel-Leede-Hess) was strongly positive. The clotting time was seven minutes, and clot retraction was normal at one hour and at the end of twenty-four hours. The recalcification time was two minutes and twenty-eight seconds and a thromboplastin generation test in which the patient's platelets were used was normal. The prothrombin time was normal (Tables I and II).

X-ray of the chest revealed moderate left ventricular enlargement and an intravenous pyelogram was normal. Cystography and retrograde pyelography

showed no abnormalities. An electrocardiogram showed left ventricular hypertrophy.

During the first five hospital days the patient was stuporous and incontinent. On the sixth hospital day treatment with antihypertensive agents including parenteral reserpine and pentolinium tartrate was started. During the next several days the patient's blood pressure fell from levels of 240-290/140-190 to 120-180/80-130 and the parenteral therapy was replaced by oral reserpine, pentolinium tartrate, hydralazine and chlorthiazide with maintenance of the blood pressure at normal levels. The patient became more alert and his vision slowly improved over the next two weeks. The papilledema disappeared and the retinal hemorrhages resolved. Urinalysis showed no

TABLE II
Results of the Thromboplastin Generation Test on Patient J.F.

Time in Minutes	2'	4'	6'	8'
Control				
Control barium sulfated plasma	60"	30"	15"	14"
Control aged serum				
Brain extract				
Patient				
Patient's barium sulfated plasma	20"	18"	17"	16"
Patient's aged serum				
Brain extract				
Control plus patient's platelets				
Control barium sulfated plasma	55"	15"	13"	—
Control aged serum				
Patient's platelets				
Control plus control platelets				
Control barium sulfated plasma	50"	16"	12"	—
Control aged serum				
Control platelets				

proteinuria and the sediment contained only occasional red blood cells per high-powered field. On the thirteenth hospital day the bleeding time became normal (four minutes and thirty seconds) and the tourniquet test negative. Urinary catechol amines were normal on two occasions.

The patient was discharged and has been maintained on oral antihypertensive therapy to the present time. His vision has steadily improved and he has been able to return to his work as a draftsman. Repeated coagulation studies including bleeding time and tourniquet test are normal.

DISCUSSION

The strong family history of cerebral and cardiovascular disease and the patient's long history of an elevated blood pressure are in favor of the diagnosis of essential hypertension. His symptoms at the time of admission were related to the accelerated phase of his hypertension complicated by a bleeding

abnormality. Laboratory studies did not indicate any underlying cause for his hypertension and a coagulation workup revealed an unexplained, markedly prolonged bleeding time, together with a positive tourniquet test. He was under no therapy when his bleeding began. With intensive antihypertensive therapy the symptoms and fundoscopic findings of malignant hypertension regressed and the bleeding abnormality simultaneously disappeared. A major problem that confronts us here is to explain the mechanisms by which his prolonged bleeding time developed.

The factors that control the bleeding time are poorly understood. The abnormality most commonly associated with a prolonged bleeding time is a deficiency or abnormality of the platelets (6). The patient's platelets were normal in number and appearance on microscopic examination. His clot retraction was normal and a thromboplastin generation test, in which the patient's platelets were used, was normal. These tests rule out a platelet abnormality as the cause of the prolonged bleeding time in this patient.

A prolonged bleeding time may be seen in some forms of vascular purpura. Cutaneous bleeding may be spontaneous or occur after minimal trauma. The increase in hydrostatic pressure within the vessels of the lower extremities accounts for the predilection of spontaneous purpura to occur in dependent portions of the body. Intramuscular and intra-arterial hemorrhages are less common. The platelets are normal in number and function. The tourniquet test is usually positive, and in those disorders in which the bleeding time is prolonged, the prothrombin consumption and thromboplastin generation may also be mildly abnormal (7).

A prolonged bleeding time due to an inherited vascular defect is seen in Von Willebrand's disease (8, 9). The absence of previous bleeding during surgery tends to rule out an inherited disorder in the patient presented. In Von Willebrand's disease the prolongation of the bleeding time appears to be due to a vascular deficit (10, 11), with the prolonged clotting time secondary to an antihemophilic globulin deficiency (9, 12). However, a prolonged bleeding time is not present in pure vascular purpura such as Henoch-Schönlein purpura (13) or scurvy (14). In Von Willebrand's disease the bleeding may therefore be due to a failure of otherwise normal capillaries to contract. Quick (15) has suggested that the abnormality responsible for the prolonged bleeding time in Von Willebrand's disease is an unknown plasma-factor deficiency similar to that seen in thrombocytopenia. The prolonged bleeding time seen in this patient may have been due to a similar plasma-factor deficiency which was precipitated during the accelerated phase of his hypertension and relieved by the control of his hypertension.

Vascular purpura may be associated with uremia or diabetes (7). The presence of normal blood urea nitrogen and creatinine in this patient eliminates uremia as a cause for his bleeding. A normal glucose tolerance test rules out diabetes mellitus as a cause of his vascular purpura.

Reserpine can cause a depletion of platelet serotonin (16). Careful inquiry

revealed no prior reserpine therapy and furthermore the patient improved while he received parenteral reserpine.

There are no reports in the literature of coagulation studies of other patients with a prolonged bleeding time during the accelerated phase of hypertension. This may be due to the rarity of this complication or the failure to perform coagulation studies on these patients. Coagulation studies including a properly done bleeding time on other patients with malignant hypertension are suggested.

SUMMARY

This is the first reported case of a patient with malignant hypertension and bleeding due to a prolonged bleeding time. The known causes of a prolongation of the bleeding time are reviewed briefly and a theory is presented to explain the bleeding abnormality in this patient. It is hoped that this report will encourage others to search for coagulation deficiencies in patients with accelerated hypertension.

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RADIOLOGICAL NOTES

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CASE NO. 235

A 27 year old female complained of persistent painful swelling of the left knee. Seven years previously a hemorrhagic effusion developed in the left knee without antecedent trauma. Multiple intra-articular injections of corticosteroids relieved the associated pain but bloody effusion continued to recur. Radiographic examination revealed marked synovitis. Six years ago, a posterior synovectomy was performed and the diagnosis of pigmented villonodular synovitis was established histologically. There was partial relief of pain but hemorrhagic effusions continued to occur. Radiographic examination of the knee was again performed (Figs. 1A, 1B) and revealed marked enlargement of the synovial shadows in the suprapatellar and infrapatellar zones, but only slight prominence of the synovial shadows posteriorly in the popliteal region where the synovectomy had been performed. There were no bony abnormalities and the articulating surfaces were smooth. Three years ago there was continued pain, marked swelling and marked limitation of motion. A needle aspiration of the anterior synovium was performed; all histologic material was then reviewed and the diagnosis of pigmented villonodular synovitis was confirmed. Radiation therapy was prescribed and the patient received 3,200 roentgens exposure dose of 2 MVP radiation. The response was not dramatic but symptoms abated somewhat and the swelling also decreased. However all symptoms recurred with severity two years ago, eighteen months following radiation therapy, and radiographic examination of the knee was again performed (Figs. 2A, 2B). Marked synovial reaction was again noted, and in particular there was increased soft tissue shadow posteriorly. A few small erosions of the subcortical bone were noted.

During the past two years, the symptoms have been persistent, severe and progressive. Clinical examination at present revealed a markedly swollen, boggy knee, with considerable heat present. The slightest motion of the joint was markedly painful. There were no systemic signs and all other joints were normal.

Radiographic examination of the knee at the present time (Figs. 3A, 3B, 3C) revealed marked synovial thickening, numerous foci of bone destruction on both sides of the knee joint with some surrounding osteosclerosis, and moderate narrowing of the articular cartilage. Although it was the clinical impression that a fusion of the joint will ultimately be required, a repeat synovectomy will be performed in an attempt to provide this young patient with a period of relatively pain-free motion.

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DISCUSSION

Pigmented villonodular synovitis, bursitis and tenosynovitis were described by Jaffe and co-workers in 1941 (1). The name of the disease accurately reflects the pathologic process in which there is exuberant synovial proliferation



Case 235, Fig. 1A. Tunnel view of the knee performed six years ago shows no bony or articular abnormality.

in a villous-like and nodular conformation; pigmentation is secondary to hemorrhagic effusion and deposition of hemosiderin (1, 2). The disease is almost always monarticular in distribution (3), has no sex predilection, and is usually found in the third to fifth decades, although the age spectrum is much wider (2, 4, 5). The knee is by far the most common joint affected. The etiology is unknown. Two important clinical features which should be emphasized are the nodular masses about the joint which are often palpable and the bloody joint effusions.

Radiographic features reflect the pathological process. The synovial proliferation may exhibit a nodular or lobulated outline and it has been stated that the increased iron pigment enhances detection of the synovial process (3). When major joints are involved the process is most often intra-articular but may be para-articular on occasion (6). Bony erosions are sometimes not em-



Case 235, Fig. 1B. Lateral view reveals marked soft tissue swelling in the suprapatellar region and infrapatellar region (arrows A and B). A moderate but well-defined soft tissue swelling is also seen posteriorly (arrow C).

phasized in the literature, but numerous reports have described or demonstrated single or multiple subcortical bony defects generally ranging up to 2 cm in size and with thin surrounding marginal sclerosis (2, 3, 4, 7, 8). The bony changes demonstrated in the case presented appear to be much more extensive than usually described. The documented sequence of their appearance is also of interest in emphasizing the unrelenting progressive course which the disease may follow despite the accepted surgical and therapeutic measures (8, 9).



Case 235, Fig. 2A. Anteroposterior examination performed 2 years ago, 18 months following a course of radiotherapy, reveals a small erosion adjacent to the medial tibial plateau in a para-articular location.



Case 235, Fig. 2B. Lateral view again reveals soft tissue swelling, but at this time there is a marked increase in the posterior soft tissue mass (arrows A, B, and C). A small subcortical lucent defect can also be seen (arrow D).



Case 235, Fig. 3A. Anteroposterior examination of the knee at the present time reveals narrowing of the joint cartilages and numerous rounded subcortical lucent defects. The defects range from 3 to 15 mm in size and are located on both sides of the knee joint. There is some associated marginal bony sclerosis.



Case 235, Fig. 3B. Tunnel view reveals similar findings. Prominent para-articular erosive lesions are particularly well demonstrated.



Case 235, Fig. 3C. Lateral view with soft tissue technique accentuates the marked soft tissue swelling about the joint (arrows A, B and C).

Other radiographic features include the prominent lack of bone atrophy, hypertrophic changes, narrowing of the joint cartilages and reactive bone sclerosis (other than the margins of bony erosions) except in advanced chronic cases. The absence of soft tissue calcifications is an important differential feature. Calcifications point to a consideration of synovial osteochondromatosis or synovial sarcoma (see Case No. 236) and virtually exclude pigmented villonodular synovitis (10). Tuberculosis also figures prominently in the differential diagnosis.

Case Report: PIGMENTED VILLONODULAR SYNOVITIS OF THE KNEE.

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CASE NO. 236

A 38 year old male complained of pain in the left knee of nine months' duration. The onset of the pain was insidious without known trauma and the symptoms gradually increased in severity. Radiographic examination of the knee three months prior to admission revealed evidence of a synovial reaction in the knee. No bony abnormality was noted and the articulating surfaces were smooth. Re-examination of the knee at the time of admission revealed similar findings. Clinically, the knee showed no undue heat or redness but there was boggy swelling and some limitation of motion. Routine examinations of the blood and urine were normal.



Case 236, Fig. 1. Lateral view of the left knee reveals soft tissue swelling filling the suprapatellar bursa (along arrows). Within the bursal region are distributed faint, tiny, punctate calcifications. There are no associated bony abnormalities.

At surgery, marked thickening of the synovial reflections was noted throughout the joint with tiny, firm projections diffusely distributed on all surfaces. These felt almost like sandpaper to the touch. A partial synovectomy was performed.

Grossly, the pathologist described the synovium as measuring up to 1 cm in diameter and having a nonpigmented nodular appearance. Histologically, the mesothelial lining was hyperplastic and there were nodular cartilaginous projections. Small focal areas of calcification were noted within the cartilage. Cultures of the joint content showed no evidence of tuberculosis or other inflammatory disease. The pathologic diagnosis was synovial osteochondromatosis.

Following operation, additional radiographic studies of the knee were performed with soft tissue technique. In the lateral view (Fig. 1) there were noted extremely faint punctate calcifications distributed throughout the suprapatellar space. These were not noted on the original radiographs which had been performed with more penetrated technique.

Clinical evaluation three months after operation revealed painless motion with some limitation at the extremes of flexion and extension. The patient walked with a slight limp but was back to work full time and on his feet all day.

DISCUSSION

Synovial osteochondromatosis, often called synovial chondromatosis, is a disease in which the synovium undergoes metaplasia and produces cartilage (1). The cartilaginous foci present as excrescences and may subsequently break off to become loose bodies in the joint. These bodies tend to enlarge and often undergo calcification and even ossification. The disease apparently is self-limited and eventually reaches an inactive stage. At that point only a presumptive diagnosis can be advanced since most pathologists demand histologic evidence of active cartilage production before making a positive diagnosis (1, 2). The disease occurs mostly in males between the ages of 30 and 50 years, but has been reported in a much wider age spectrum. The knee joint is most commonly involved and the process is almost always monarticular in distribution.

Fine soft tissue calcifications are a radiographic hallmark but are frequently extremely difficult to demonstrate. When present, the differential diagnosis lies between synovial osteochondromatosis and synovial sarcoma. The latter is usually para-articular rather than intra-articular and tends to destroy rather than erode bone; in many cases, however, the differential diagnosis may be impossible. When many calcified loose bodies are present, the differential diagnosis should include severe hypertrophic osteoarthritis and neuropathic joint disease. In the absence of calcifications, pigmented villonodular synovitis and a specific joint infection such as tuberculosis must be considered (1, 3).

Case Report: SYNOVIAL OSTEOCHONDROMATOSIS OF THE KNEE.

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Case 237, Fig. 1A. Supine examination of the abdomen performed approximately one hour after birth shows a conspicuous absence of normal gas-containing bowel. Only two small collections of gas are noted, both apparently in the stomach in the left upper quadrant (arrows). A very large soft tissue mass occupies the entire abdomen and bulges into the right flank. No abnormal calcifications are noted. (A static artifact is noted on the lower portion of the film.)

CASE NO. 237

A newborn male infant, the product of an uneventful pregnancy and delivery, was noted at birth to have a markedly protuberant abdomen. The consulting surgeon described the abdomen as containing a large soft mass which presented to the right of the midline but which extended into the right flank and to the left across the midline. The mass was not mobile and no lobulations were felt. The consistency suggested a cystic quality but this could not be stated with certainty.

Radiographic examination of the abdomen was performed approximately

one hour following delivery (Figs. 1A, 1B). A large homogeneous soft tissue mass was noted to occupy the abdomen which bulged into the right flank but not the left. No calcifications were noted. Two tiny collections of gas were noted in the left upper abdomen apparently in the stomach. The abdomen was



Case 237, Fig. 1B. Right lateral projection of the abdomen delineates the large mass bulging the anterior abdominal wall. Two small collections of gas are again noted in the upper abdomen (arrows).

otherwise devoid of gas. Since the infant was vigorous and cried well, the findings were felt to be indicative of gastric obstruction apparently related to the mass.

The infant failed to pass urine or meconium and respirations became labored. Abdominal exploration was performed at eleven hours of age. A grapefruit-sized cystic mass was found retroperitoneally behind the right colon. The stomach and intestines were markedly displaced and compressed. The ureter was traced to the mass and the surgeon felt that the mass represented a hy-

dronephrotic kidney or a very large renal cyst. The left kidney was normal to palpation. A right nephrectomy was performed.

The baby did well postoperatively and had normal respiratory, urinary and gastrointestinal functions. Intravenous urogram was performed at ten days of age and revealed good function of the left kidney with no gross abnormality.

The pathologist described a large retention cyst of the kidney. Along one wall of the cyst was a thin mantle of underdeveloped tubules and glomeruli but the main wall of the cyst was composed of dense fibrous connective tissue. Longitudinal sections through the upper ureter revealed large fibrous folds covered by epithelium which could be interpreted as valves. Although it was felt that the mass represented a large simple cyst, a hydronephrotic sac secondary to ureteral obstruction by valves could also explain the pathological findings. There was no evidence of neoplastic or polycystic disease.

DISCUSSION

Radiographic examination of a normal newborn infant at one hour of age should reveal gas extending down past the stomach into the small bowel. Exceptions to this rule are usually in cases with poor or absent crying or persistent lying in the prone position (1). Since these exceptions do not apply in the case presented, the gas pattern indicates a mechanical obstruction at the gastric level. It is often not emphasized that a large mass extrinsic to the gastrointestinal tract can cause obstruction due to compression or angulation. An excellent example of duodenal obstruction due to a large renal mass has recently appeared in the radiographic literature (1). Gastric obstruction is apparently much less common, presumably because of the greater size and mobility of the stomach as well as its anterior location.

Introduction of air into the stomach via a nasogastric tube would have been helpful in clarifying the gastric shadow.

Case Report: CONGENITAL CYST OF THE RIGHT KIDNEY WITH GASTRIC OBSTRUCTION.

ACKNOWLEDGMENT

The editors wish to thank Dr. Sheldon B. Adler, Good Samaritan Hospital, Suffern, N. Y., for permission to use this case.

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CASE NO. 238

This 29 year old female was told that as a child she had suffered from "Celiac Disease." She had been well until one month before her present illness when she noted the sudden onset of ten watery bowel movements per day unaccompanied by pain or vomiting. There had been no blood in the stools. Her appetite had remained good, although she had noted a five pound loss of weight.

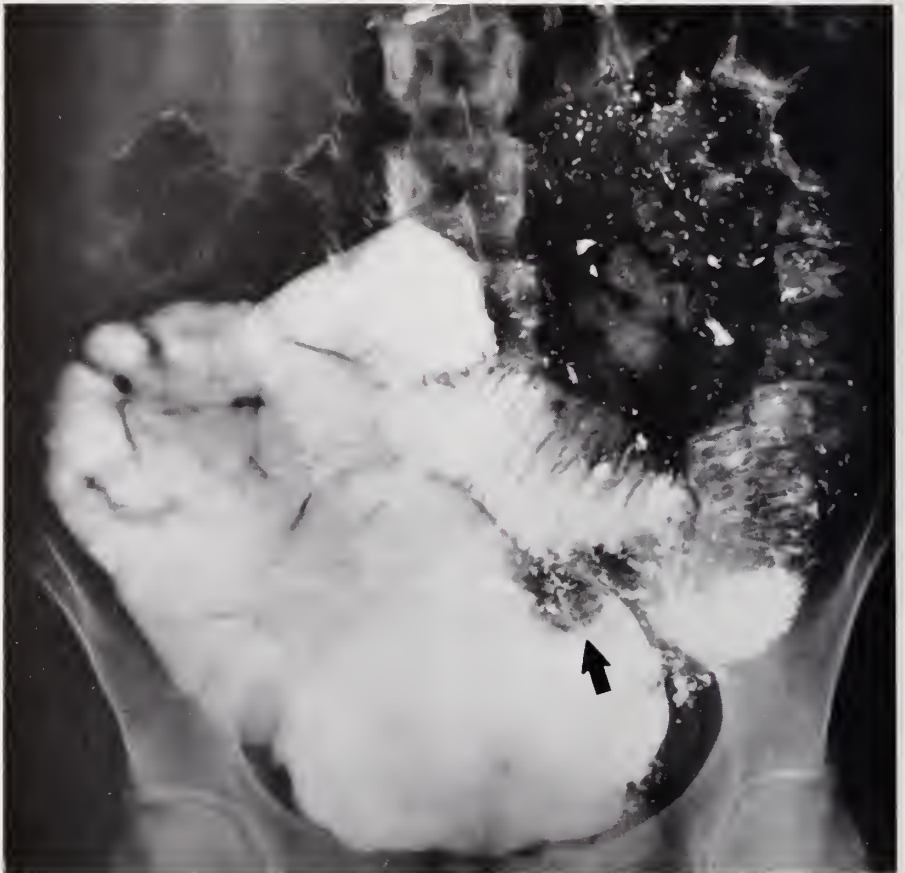
Because of these complaints, a barium enema was performed which showed no organic abnormalities of the large intestine. The bowel was normally distensible. No ulcerations were seen. On the right side of the colon, there were some irregularities of the contour (Fig. 1), but this was apparently due to a



Case 238, Fig. 1. Barium enema reveals irregularity of the contours of the right side of the colon. This is due to a marked amount of secretions pouring in from the small bowel. On repeat examination a few days later the contours appeared normal. The terminal ileum is filled by reflux and appears normally distensible and of normal caliber.

marked amount of secretions within the bowel as on repeat examination the colonic contours were smooth. Because of the normal barium enema, a small bowel examination was performed. The proximal jejunum was noted to be moderately dilated, but on the early films it contained no unusual amount of secretions. The valvulae conniventes were normally pliable. In later films, the dilatation previously noted appeared to be more marked in the distal jejunum and proximal ileum. This was associated with flocculation and seg-

mentation of the barium column. An ill-defined filling defect was noted in the distal jejunum (Fig. 2A). Pressure spot films of this area revealed a well-defined filling defect in the distal jejunum associated with a coil-spring appearance of the adjacent bowel, typical of an intussusception (Figs. 2B, 2C). This



Case 238, Fig. 2A. Radiograph of the small intestine in the prone projection four hours after the ingestion of barium reveals marked dilatation of the distal jejunal and proximal ileal loops. This is associated with flocculation and segmentation of the barium column. An ill-defined filling defect is noted in the distal jejunum (arrow).

was noted on several films. There was no evidence of obstruction to the flow of barium in this region. Pressure spot films of the terminal ileal loop appeared normal.

The patient was hospitalized and numerous tests were performed which included stool examination, prothrombin time, absorption tests, and jejunal biopsy; these confirmed the diagnosis of a malabsorption syndrome.

The patient was placed on a gluten-free diet and showed remarkable improvement in her symptoms.

DISCUSSION

The classical features of sprue are well known and include small intestinal dilatation, segmentation, fragmentation and moulage formation. Dilatation is

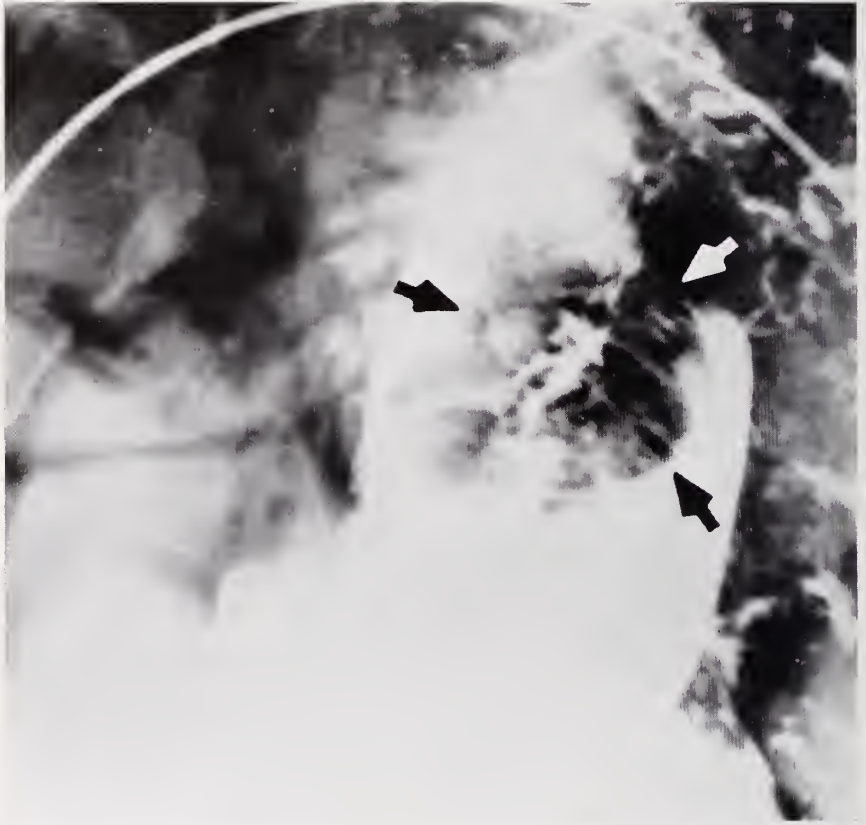


Case 238, Fig. 2B. A film taken half an hour later with a pressure paddle in the region of the distal jejunum reveals the filling defect to better advantage (arrow).

the most constant roentgen finding and is often the only recognizable abnormality in this disease (1).

Beside the classical signs outlined above, the case presented exhibited an additional, seldom described finding in the distal jejunum and proximal ileum—namely, transient intussusceptions. Whereas 90 per cent of the intussusceptions in infants and children are of the idiopathic variety, 80 per cent of those in adults are secondary to demonstrable organic causes. Fifty-five per cent of all intussusceptions in adults are due to small bowel tumors. The mechanism

or formation of the idiopathic intussusception is not clear, but it is felt to be due to a proximal wave of contraction adjacent to a distal segment of relaxation (2). Some think that it is related to an adenovirus infection with hypertrophy of the lymphoid elements in the wall of the small bowel which in turn form the head of the intussuscepiens (3). In sprue, it is probable that the cause



Case 238, Fig. 2C. Spot film at the same time reveals typical "coil-spring" appearance associated with the smooth intraluminal filling defect (between arrows).

of the intussusception is related to the dilatation of the small bowel which is filled with a large amount of secretions.

As was the case in the patient described above, transient intussusceptions in sprue seldom produce a clinical picture of crampy abdominal pains and vomiting. In those cases of transient intussusception described by Teitelbaum in children, the patients usually presented with classical episodic abdominal pain and vomiting (4).

The presence of transient intussusception in association with sprue is not mentioned in any of the classical papers on sprue or in the discussions on the etiology of intussusception in adults. However, it is being noticed with in-

creased frequency in this disease. It is imperative to recognize the presence of the sprue pattern when multiple intussusceptions are seen on small bowel examination, so that these are not misinterpreted as representing intussusceptions secondary to small bowel tumors.

Case Report: TRANSIENT INTUSSUSCEPTION IN SPRUE.

ACKNOWLEDGMENT

The editors wish to thank Dr. Samuel K. Elster for permission to use this case.

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CASE NO. 239

This 68 year old male presented with a nontender swelling of the forehead of one month's duration. There had been no history of previous trauma. The patient complained of no systemic symptoms. He had noted the mass to increase in size slowly in the past four weeks.

Physical examination disclosed a 4×5 cm nontender firm soft tissue swelling occupying the midportion of the forehead near the bregma. The overlying skin appeared to be stretched but was not reddened or otherwise abnormal. The remainder of the physical examination was negative except for a large firm axillary lymph node on the left side.

Biopsy of the left axillary mass revealed small cell lymphosarcoma. The patient was started on a course of cobalt-60 radiotherapy directed to the left axilla and to the swelling on the forehead. Both masses showed some decrease in size at the end of treatment.

Radiographic examination of the skull revealed a smooth well-demarcated soft tissue swelling in the superior portion of the frontal bone in the midline. Tangential soft tissue film reveals minute perpendicular striations of the outer table of the frontal bone under this soft tissue swelling (Fig. 1A). The diploic space and the inner table were normal (Fig. 1B). In the frontal view, there were no apparent abnormalities (Fig. 1C).

DISCUSSION

This case, in all probability, represents an instance of a lymphosarcomatous lesion within the scalp with secondary involvement of the underlying frontal

bone. Bone involvement of the skull in lymphosarcoma is rare, but when it occurs it usually presents as an area of bone destruction similar to that seen in metastatic carcinoma (1). When the soft tissues are primarily involved as in the case presented, a most unusual appearance to the underlying outer table is noted which is quite different from the usual lytic lesion of the skull. It is probably the result of invasion of the pericranium and the outer table by ma-



Case 239, Fig. 1A. Lateral soft tissue radiograph of the frontal region reveals a smooth soft tissue swelling with intact tissue planes. There is a fine layer of periosteal new bone formation of the perpendicular striated type seen adjacent to the outer table. This is seen to extend over the entire area of the soft tissue swelling.

lignant cells with a reactive periostitis (2, 3). In the differential diagnosis, one must include osteogenic sarcoma, primarily arising in the parosteal elements. Also a peculiar hemangioma of the skull can produce a similar appearance. Neuroblastomas occurring in children may, on occasion, present with a large

Case 239, Fig. 1B. The same area using hard technique reveals that the inner table and the diploic space in the region of the lesion are normal.

Case 239, Fig. 1C. Caldwell view reveals no further abnormalities of the frontal bone.



Fig. 1 B.



Fig. 1 C.

soft tissue swelling with a spiculated area of periosteal reaction, but in this case there is a large associated destructive process involving the entire thickness of the diploë. Meningiomas may produce a peculiar exostosis which superficially may resemble the case described; but when this is associated with a large soft tissue mass, there are other stigmata of this disease, namely increased vascularity of the adjacent bone and a bony defect involving the inner table and diploic space.

Case Report: LYMPHOSARCOMA OF THE SCALP WITH BONY INVASION.

ACKNOWLEDGMENT

The editors wish to thank Dr. Samuel K. Elster for permission to use this case.

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RUDOLPH KRAMER, M.D.
1892-1964

In Memoriam

RUDOLPH KRAMER

1892-1964

Dr. Rudolph Kramer was an eminently skilled laryngologist and a superb endoscopist. His early indoctrination in pathology, as a post-graduate student in Paris, Berlin and Vienna, helped him to become an excellent teacher of the basic knowledge of the pathogenesis of diseases of the ear, nose and throat. As Director of Otolaryngology at The Mount Sinai Hospital from 1931 to 1954, he made several significant, basic contributions to his specialty. Amongst these were his fundamental studies in the anatomy of the tracheobronchial tree with correlation of the pulmonary segments and the branch bronchi. His original dissertation on benign bronchial tumors and their differentiation from adenocarcinoma of the bronchus was an important contribution, now part of the working knowledge of our profession.

With Dr. William Harris, he was a pioneer in this country in the treatment of carcinoma of the larynx by radiotherapy. Although a surgeon, Dr. Kramer departed from the accepted surgical treatment of carcinoma of the larynx by initiating a new modality of therapy by radiation. This bold venture gained national acceptance and remains of great value today.

Dr. Kramer was a shy, retiring man, possessed of great humility and modesty despite his many professional and personal accomplishments. Many of his residents profited from his benevolence. He was eager to help without thanks or recognition of his service.

Dr. Rudolph Kramer remained a student and scholar throughout his life. He was a prolific reader, a talented musician—as well as being well versed in such diverse topics as nuclear energy, mathematics and gardening. Dr. Kramer was a man of utmost integrity who never compromised with the truth as he saw it. He not only encouraged his residents to become productive but helped secure the necessary facilities for their research and advancement. Dr. Kramer leaves his mark as a physician who made pioneer contributions to his specialty, aided his students immeasurably and whose integrity and modesty inspired all who knew him.

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HAROLD NEUHOF, M.D.
1884-1964

In Memoriam

HAROLD NEUHOF

1884-1964

Dr. Harold NeuhoF, Consultant Surgeon and Director Emeritus of the Department of Surgery at The Mount Sinai Hospital, died in Tucson, Arizona, on January 7, 1964, of injuries received in an automobile accident the preceding day. He was in his eightieth year. His passing was indeed untimely, for, despite his years, he had remained the same dynamic personality we all knew.

Harold NeuhoF received his medical degree from the College of Physicians and Surgeons of Columbia University in 1905, at which time he began his professional career at Mount Sinai. During the four years of his internship and his residency in the Private Pavilion, he had two of the greatest surgeons of that era as preceptors, namely, Dr. Arpad Gerster and Dr. Howard Lilienthal.

He received an appointment to the P & S Division of the Surgical Service at Bellevue Hospital in 1910. In World War I, he served overseas with the Presbyterian Hospital Unit, Base Hospital # 2, and it was during that period that Harold became interested in the field of neurosurgery. Upon his return to civilian life, he was appointed Associate Surgeon at Mount Sinai on the service of Dr. Charles A. Elsberg. He soon realized, however, that thoracic surgery was his *métier* and, when Doctor Lilienthal retired, Harold was placed in charge of the patients requiring thoracic surgery. He was appointed Surgeon to the Hospital in 1930, which rank he held until 1946, when he was appointed Consultant Surgeon.

Harold was also a member of the Neurosurgical Service at Montefiore Hospital from 1913 to 1923, at which time he was appointed Attending Surgeon and Chief of the Surgical Division. He resigned from Montefiore in 1932, after having established the Thoracic Surgical Service, and was then appointed Consultant Surgeon.

At the age of sixty-two years, upon his retirement from The Mount Sinai Hospital, Harold was invited to become Director of the Division of Surgery at the Beth-El Hospital (now the Brookdale Medical Center) in Brooklyn, and to reorganize the department. He retired from that position when he reached the age of seventy-five years, but he continued there in research and was preparing a clinical project for the prevention of postoperative thrombosis and embolization by the administration of minimal doses of anticoagulants.

Present-day surgical progress has proved that Harold NeuhoF was many decades "ahead of his time." In a monograph entitled "The Transplantation of Tissues," published in 1923, he described an operation he had performed in 1917—the transplantation of the kidney of a lamb into a woman whose kidneys had been rendered functionless by bichloride of mercury, and who survived the operation for five days.

At Mount Sinai, he developed one of the most outstanding thoracic surgical services in the country. In collaboration with his co-workers, an entirely new

concept of abscess of the lung was formulated. Their contributions concerning the etiology, bacteriology, pathologic anatomy, roentgenographic features, clinical course, and surgical treatment of putrid lung abscess formed the basis for a universal understanding of a new symptom complex.

There was no aspect of thoracic surgery in which Harold was not interested and, being a most prolific writer, his many contributions to the literature on carcinoma of the lung, mediastinitis, and thrombophlebitis, as well as those on pulmonary suppuration, covered the entire field.

His creative mind incessantly developed ideas which inspired his co-workers, and his enthusiasm, zeal, and inexhaustible energy constantly evoked wonderment and admiration. He was a hard taskmaster, yet never would he ask anyone to do that which he, himself, would not do. The profound interest he evinced in the professional development and growth of the members of his staff was only one of the many qualities that constituted the measure of the man and endeared him to the younger surgeons.

Dr. Harold Neuhoof was a founder member of the American Board of Surgery and of the American Board of Thoracic Surgery. He was a Fellow of the New York Academy of Medicine and of the American College of Surgeons, as well as a member of the American Association for Thoracic Surgery, the American Surgical Association, the New York Surgical Society, the New York Society for Thoracic Surgery, and of the New York Society for Cardiovascular Surgery. He was Clinical Professor of Surgery at Columbia University.

We condole with his widow, Olga, and his children, Marion, Marcus, and Joan, on his sudden passing and we express to them our heartfelt sympathy. May they find solace in the knowledge that he was blessed to continue his professional activities to the end, his fourscore years replete with scientific achievements; and above all, that he had the undying affection of his staff and of his many colleagues to whom the memory of "Skippy" will always be a source of inspiration.

"The rung of a ladder was never meant to rest upon, but only to hold a man's foot long enough to enable him to put the other somewhat higher."

ARTHUR S. W. TOUROFF, M.D.

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SYMPOSIUM
ON
OBSERVATION

Saul Jarcho, M.D.

Guest Editor

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INTRODUCTION

The giant Antaeus constantly renewed his strength by contact with the earth. In the same way we physicians reinvigorate ourselves from time to time by recourse to chemistry, or physics, or physiology, or pathology. Thereby, like the fabled giant, we "keep our feet on the ground."

But more fundamental than any branch of knowledge is an attitude of mind which we must constantly keep in the prime of cultivation lest the weeds and thistles of indolence overgrow the ground. The attitude to be desired is a complex one, in which we can readily isolate two components, *viz.*, a receptivity to new ideas and the capacity to make fresh observations. It is the latter—observation—to which this symposium is dedicated.

The collection of essays herewith set before you has been designed for the physician. Chapters have been requested from clinicians, laboratory scientists, and historians, all of whom offer their best thoughts, which are the product of minds sharpened by thought and experience.

It will be noticed, especially in the essays contributed by clinicians, that a degree of overlap exists in the scope of discussion. This has been done deliberately, since experience is cumulative and the experience of reading a *series* of clinical writers cannot fail to be beneficial to the attentive reader.

Literature is one of man's blessed tools. We hope that this symposium will serve you well.

Saul Jarcho, M.D.
Guest Editor

The Mount Sinai Hospital
New York, July, 1964

The Exercise of Observation in Forensic Medicine

MILTON HELPERN, M.D.*

New York, N. Y.

Sudden, suspicious and violent death is a subject for official investigation in the United States. As in Great Britain and throughout the British Commonwealth and the countries which formerly were part of it, it constitutes the only medical problem entirely under official jurisdiction. The fatal categories have been expanded to include unexpected deaths of persons in apparent health, those in which there is a suspicion of violence, fatal poisonings, deaths of persons in legal custody, deaths from abortion and those occurring under unusual circumstances. In accordance with the statute and by long accepted practice in the City of New York, any death in which a traumatic injury or poisoning is a possible partial causative factor must be officially investigated whether the traumatic component is the result of criminal assault, accident or suicidal attempt, any of which may have legal implications. The broad provisions of the medical examiner's law were established to ensure the official determination of the cause of all deaths which are of immediate concern to the community, the relatives of the deceased person, and the law enforcement agencies, and are important for the proper administration of justice.

New York City also provides an additional safeguard to ensure the official investigation of all deaths requiring it by the simple procedure of screening every death certificate by the Burial Permit Division of the Department of Health before the body of any deceased person who was under medical care and died in the home or in the hospital can be removed from the place of death. Such screening assures the reporting to the medical examiner's office of those deaths in which the attending physician does not appreciate the need for referral. Most physicians, whether in private or hospital practice, have relatively few fatalities among their patients. These may occur at long intervals of time during which the physician may forget the variety of deaths that are reportable for official investigation. Without any ulterior purpose he may inadvertently fail to report to the medical examiner a death in which there was a definite or possible traumatic component.

In New York City deaths caused by chronic as well as acute poisoning of one type or another, including the effects of alcoholism and those associated with addiction to drugs, and unexpected deaths during diagnostic, therapeutic, surgical and anesthetic procedures sometimes designated euphemistically as therapeutic misadventures, are all reportable. The Medical Examiner's Office now investigates 30,000 of the approximately 90,000 deaths occurring in the city each year. Of these approximately 4,000 are inquired into and then referred back to the attending physician for certification as deaths from natural

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causes. Investigation of cremation requests already certified accounts for 3,000 cases. In the remaining 23,000 cases the scene of death is investigated and the body examined there by a medical examiner or medical investigator, who must decide from the circumstances whether or not an autopsy and other related examinations are indicated to establish definitely the cause of death and other findings, or that the death can be certified from the circumstances and external examination of the body without autopsy. When an autopsy is considered necessary it must be performed by a medical examiner who by law is required to be a skilled pathologist and microscopist. In recent years the law has been amended to require the medical examiner to include necessary histologic, toxicologic, serologic and microbiologic examinations in order to determine the cause of death more accurately and to establish other findings relevant to issues which may subsequently arise in the development of the case. When there is indication or suspicion of criminal violence, the autopsy must be witnessed by at least one other medical examiner.

The determination of the cause of death is perhaps the most important but not the only purpose of the post mortem investigation and autopsy. It may be obviously simple but in numerous cases it is dependent as much if not more so on a careful consideration of the circumstances determined from the investigation before and sometimes after the autopsy. It should be evident that the investigations and autopsy must be carried out with reasonable promptness if a death is to be fully resolved. When correlation of circumstances and autopsy observations have produced an answer requiring action, it is not sufficient for a medical examiner quietly and passively to certify the cause of death for reference and statistical analysis. It is of the utmost importance that he alert other appropriate investigative and corrective agencies and provide them with the information. Medical examiner's findings and conclusions are of immediate significance to the community and cannot be passed off politely as merely interesting or unusual without communication. More of the medieval "hue and cry" are needed.

The processes of observation in forensic medicine have many ramifications and give rise to many problems. It is rather remarkable that in some instances the pathologist observes and describes the findings of an autopsy correctly but completely misinterprets what he sees, with resultant serious error in his conclusion. This is exemplified in the following case from another jurisdiction.

A 50 year old man who was employed as a parking-lot attendant awoke one morning with abdominal cramps and diarrhea. He did not feel ill enough to remain at home but insisted on going to work. His wife called a physician, who prescribed bismuth subcarbonate and Kaopectate which he picked up at the neighborhood pharmacy on the way to work. Shortly after arriving there he drank a mouthful of each medication. Instead of being relieved his symptoms became much worse and he then returned home. His wife, who had been a trained nurse, recognized the seriousness of his illness and again called the physician, who arranged for his admission to the local hospital. There his condition rapidly worsened; vomiting, increasingly severe diarrhea, abdominal

pain and shock supervened. Death occurred several hours after admission. The hospital asked and received consent for an autopsy from the wife and this was performed by the hospital pathologist, who noted and accurately described an acutely reddened and hemorrhagic gastric mucosa with evidence of irritation in the intestinal tract, and marked pulmonary congestion and edema with congestion of the remaining organs. Microscopic examination of the tissues confirmed the gross findings but despite the fact that no primary anatomical cause of death was recognized, the death was certified as having resulted from "idiopathic pulmonary edema." No other examinations were made in connection with the autopsy. As is often the case, the impressive word, "idiopathic" resulted in the death certificate being approved and the death being considered natural. The death was not reported for official investigation.

In all probability the true cause of death in this case would never have been discovered had it not been for the fact that the widow several weeks later called at the hospital for her deceased husband's clothing. Had she donated the clothes to charity, as is often done in such cases, or ordered them destroyed without examining them, the case would not have been solved. She took the clothes and on going through the pockets found the two bottles of medicine. It then occurred to her that her husband had become worse instead of better after taking some of each drug. She requested the state laboratory to examine the contents of the bottles and to everyone's surprise the bottle labeled bismuth subcarbonate was found to contain a mixture of 50 per cent sodium fluoride and 50 per cent bismuth subcarbonate.

At first there was suspicion that the widow had tampered with the bottles. Unknown to her the authorities obtained a prescription for similar medications which were filled at the same pharmacy. Again, to everyone's astonishment, the newly prescribed bottle of bismuth subcarbonate was found to contain 50 per cent of sodium fluoride. The pharmacy was then investigated. It was learned that the owner had only recently purchased the establishment and was dispensing bismuth subcarbonate from a supply in an old apothecary jar bearing that label. When the jar's contents were analyzed they were found to contain 50 per cent sodium fluoride. How and when this contamination occurred was never determined. A \$10,000 life insurance policy with a \$10,000 double indemnity provision was paid to the widow when the facts were revealed. Even though there was no chemical corroboration of the autopsy findings, the circumstances, clinical history and gross appearance of the stomach at autopsy were entirely consistent with acute fluoride poisoning which the pathologist had failed to recognize as a possibility. The conspicuously intense pulmonary congestion and edema are commonly observed in such acute poisonings. They are a secondary phenomenon associated with shock and not a primary disease.

A common source of error during the performance of a forensic autopsy is the failure to examine carefully and completely all parts of the body for minute wounds which are not in themselves a cause of death but indicators of the violent mechanism by which death occurred. The search for such injuries will

be guided by the circumstances under which death occurred. These circumstances can never be disregarded and it is only by their consideration that deaths from electrocution with low tension currents will be recognized. Electrical burns or current marks representing sites of contact with electrocuting sources of current may be extremely small and located on portions of the hands or feet or other parts of the body in such a way as to escape detection unless specially looked for. In some instances and under certain conditions electrocution by low tension currents can take place without any external burn representing a point of electrical contact. Whether or not an electrical burn occurs on the skin depends upon the site through which the current enters the body and on local conditions that affect and diminish the resistance of the skin where contact is made. The local burn is determined by the wattage, which is the square of the intensity or amperage of the current multiplied by the resistance. Thus an electrocuting current conducted over a wide surface may traverse the body without the production of sufficient wattage to cause a burn in any localized area. In approximately one-third of the cases of accidental electrocution by low tension current electrical burns are not encountered and the cause of death can only be determined by a consideration of the circumstances at the scene of death in conjunction with the autopsy findings. The danger of misinterpreting such cases arises from failure to investigate adequately the circumstances at the scene of death with facilities for the reliable testing of the electrical equipment in question. The manner of death in its rapidity can closely simulate death from occlusive coronary artery disease except that the victim of electrocution is apt to cry out. When one considers that he may be a man of middle age with a history of coronary artery disease, or may present at autopsy the evidences of unsuspected previously silent substantial occlusive coronary artery disease, one can appreciate how easily a misleading history or even the demonstration of severe coronary artery disease at autopsy can lead to the erroneous conclusion that death occurred from heart disease and not from electrical shock. In such cases, one has to resist pressures from family and friends to certify the cause of death without autopsy as occlusive coronary arteriosclerosis on the basis of the prior history or age of the deceased and the frequency of fatal coronary artery disease in that age group.

An analogous situation is commonly encountered in sudden and sometimes almost instantaneous deaths of middle-aged and elderly persons in whom there is a reliable or even spurious history of coronary artery disease offered to influence the medical examiner to certify the death as natural without autopsy. When such apparently natural sudden deaths occur during the partaking of a meal in company, the witnesses eating at the same table with the deceased are usually unaware of what has happened and may with good intention provide a history of coronary artery disease in the deceased. It is best to perform an autopsy in all such cases, not the kind that takes the forensic pathologist exclusively to the heart to provide anatomical evidence to confirm that the deceased had coronary artery disease. It is important in such cases to carry

out a complete autopsy which must include the throat and a careful search for an obstructing foreign body, namely a bolus of food, such as a piece of steak or turkey, or lobster tail or clam impacted in or above the larynx completely blocking the airway. The symptoms and signs manifested by a person choking to death on a bolus of food can be identical with those encountered in a death from occlusive coronary arteriosclerosis. The victim may become cyanotic or he may become pale. Systematic and thorough observation at autopsy in this type of case will easily demonstrate death by choking, an occurrence not uncommon but often unrecognized because of inadequate post mortem investigation.

Most lay people and many physicians are of the opinion that in every case the cause of death can readily be determined merely by the performance of a complete autopsy, and that this procedure more or less automatically provides the answer. In fact there are pathologists who perform forensic autopsies without taking the trouble to find out the circumstances of the death. There are many instances which illustrate the serious errors in interpretation that can occur when conclusions are based solely on observations in the dead body. An autopsy may reveal essentially negative findings which become meaningful for the determination of the cause of death only when considered with the history, as in deaths from epilepsy. In other cases, substantial pathological findings are encountered that are entirely misleading and have no relationship whatever to the cause of death. This is particularly true in cases in which a severe grade of occlusive coronary arteriosclerosis is discovered as an apparent cause of death and the real cause of death remains undiscovered. Similarly, a significant segmental occlusion of a coronary artery or other more or less subtle natural or traumatic cause of death may be overlooked and the toxicologist harassed for failing to discover a non-existent poison. Errors occur in both situations when history and circumstances are disregarded and the autopsy is not completely and skillfully performed. In many cases, the autopsy alone is sufficient to disclose an obvious unequivocal cause of death.

Electrocution and choking on a bolus of food are not evident until carefully looked for. Rapid deaths occurring from high cervical spine fractures with injuries of the spinal cord are not discovered by the pathologist who fails to look for such injuries because the case is not labeled as such. Although occlusive coronary arteriosclerosis is the most common cause of sudden and unexpected natural death in middle-aged persons, such deaths are readily simulated by traumatic or unnatural causes of death, three of which have already been mentioned. It is sometimes difficult for the medical examiner to resist the pressures against the performance of an official autopsy brought to bear by relatives of the deceased in apparently natural and nonsuspicious deaths in which there is a more or less documented history of heart disease and he is not infrequently threatened with a damage suit for exceeding his legal authority in selecting such a case for autopsy. But unsuspected traumatic injury or poisoning have been revealed so many times as a cause of death

that the forensic pathologist cannot risk overlooking them by omitting the autopsy on the basis of circumstances, history and threats.

Although most families are reasonable and appreciate the reasons for the performance of autopsies, there are some memorable exceptions. A case in point is that of an elderly woman who had taken a taxicab to the Waldorf-Astoria Hotel. When the cab pulled up at the hotel the driver turned around and found the passenger unresponsive on the floor, where she was pronounced dead. The body was then taken to the Medical Examiner's Office. Because of the circumstances it was considered necessary that the cause of death be determined by autopsy. One might add parenthetically that under other circumstances, a person of similar age dying suddenly in the presence of witnesses while seated in a chair, without the possibility of traumatic injury, might have her death certified as having resulted from natural causes without the necessity of having the precise cause of death determined by autopsy. Such deaths are certified every day on investigation and examination of the body without autopsy; but unexpected death on the floor of a taxicab in the absence of witnesses provides an unusual set of circumstances with possibilities other than natural disease as the cause of death.

The next day representatives of the family, including a lawyer, called to say that the deceased had been suffering from severe hypertension, arteriosclerosis, arthritis and a number of other complaints and that the family were very much opposed to an autopsy which they considered entirely unnecessary because of the age of the deceased, prior history of illness and absence of external signs of injury. The lawyer threatened a civil suit against the medical examiner. The possibility of a suit was considered an occupational hazard. Despite the threats, the autopsy was performed and revealed a markedly enlarged heart, severe coronary and generalized arteriosclerosis and osteoarthritis. Had these diseases been the only findings, it is very likely that the medical examiner would have been sued for having acted in an arbitrary manner and exceeding his authority. Fortunately, such a suit did not materialize for the examination of the cervical spine disclosed that the deceased had died as the result of a fracture of the odontoid process of the axis and crushing of the corresponding segment of the spinal cord. Two years later the same lawyer called the medical examiner to say that a subpoena for his appearance in court in a civil suit against the taxicab owner was being served him in connection with the death. When asked whether he was the same lawyer who had threatened to sue the medical examiner for an unnecessary autopsy on the body of a sick, elderly lady, he sheepishly replied, "Don't rub it in."

The medical examiner in addition to investigating the circumstances at the scene of death also has the responsibility of deciding that an autopsy is necessary as part of the post mortem examination and also the responsibility of performing it. If, based on his experience and the circumstances of the case he so decides, he should carefully perform the autopsy and resist pressures to the contrary regardless of how obvious or apparent the cause of death may be.

He cannot rationalize his failure to perform an autopsy which is indicated for good reasons on the basis of objection from the next of kin. The responsibility is the medical examiner's and he cannot abdicate it because of family objection in a case with a bona fide indication for autopsy.

On the other hand, there are cases in which it might be considered unreasonable and arbitrary for the medical examiner to do an official autopsy to which the next of kin are strongly opposed. The best example of this situation is that of the elderly person who falls at home or elsewhere as the result of some slight accident or bodily infirmity, sustains a fractured hip, which injury despite repair is followed by a series of complications more natural than traumatic on the basis of prior disease, and eventually dies of a combination of disease and traumatic injury. Such deaths are reportable to the medical examiner and must be certified by him because of the fracture component in the cause of death; yet it would be arbitrary to order an autopsy in such a case against the wishes of the family. But in the event the family requests the autopsy, or does not object to its performance, then it should be and usually is performed for its medical interest and value. In such cases, when death occurs in the hospital and permission is obtained for autopsy from the next of kin, and there are facilities for its performance in the hospital by a qualified pathologist, it is permissible for such an autopsy to be done in the hospital under supervision of the medical examiner who is responsible for the post mortem examination and for certification of the cause of death whether an autopsy is or is not performed.

A poorly performed forensic autopsy is worse than no autopsy at all. For in the latter instance one knows he doesn't know the answer and appreciates the limitations of the knowledge on which his conclusions as to the cause of death are based. In the former instance the autopsy is assumed to have provided the basis for a correct answer, which it hasn't, and there exists the impression that the cause of death has been accurately determined. In other words, one doesn't know he doesn't know, a situation of concealed ignorance fraught with all sorts of dangerous possibilities.

Some years ago I was asked to review a case involving the death of a high-level economist in the employ of the United States government. The deceased was a man of middle age who had been assigned to an important post in the Far East as head of an Advisory Commission. His wife was along with him on this trip. After a period of time he seemed to lose interest in his work and one morning he was found unconscious and could not be aroused. Circumstances suggested that he had taken an overdose of barbiturates. He was taken to the local hospital where his stomach was washed out and he made a fairly rapid recovery. When asked why he had taken the medication in excess, he did not deny having done so. This was taken as a tacit admission of his having taken the suspected overdose for which he was treated.

On recovering from this incident he and his wife returned to this country. He underwent a physical examination which did not disclose any organic disease. Some months later the deceased was reassigned to the same post, but this time

he made the trip without his wife. The same cycle of events occurred. After a period of responsible activity he again began to lose interest and remained away from important meetings to which he sent his subordinates instead. His loss of interest and withdrawal became more marked. One afternoon he returned home in the middle of the day, to the great concern of his associates who visited him later in the evening of the same day. He ate little that night, had several drinks and retired to bed. In the morning his servant was unable to rouse him. The circumstances were entirely similar to those in the previous incident. An empty bottle that had contained barbiturates was again found alongside the bed. He was removed to the hospital unconscious and placed under the care of the same physician who administered the same treatment which had been successful on the previous occasion but this time proved a failure. The treating physician, on the basis of the circumstances and previous admission, certified the death as having resulted from acute barbiturate intoxication. A pathologist was not available and an autopsy was not performed.

The body was then embalmed and shipped by air from this far-off island to this country where the deceased's wife arranged for an autopsy to be done by a private pathologist who evidently had not been informed and did not take the trouble to find out the circumstances surrounding the death and the history of the prior incident of unconsciousness and recovery. The autopsy was confined to the body and the report described a "thrombosis of the superior mesenteric vein" although there were no associated changes of hemorrhagic infarction in the small intestine such as one would expect if there had been an antemortem thrombosis of the vein in question. Nevertheless, death was attributed to that finding. The organs of the neck were not examined, nor was the brain removed for examination and chemical analysis. Despite the circumstances and the cause of death previously certified on the basis of the history and clinical findings, there was no attempt to determine whether an overdose of barbiturates had been ingested.

The widow sent the report of the incomplete autopsy of the embalmed body and opinion of the cause of death to the treating doctor who had originally certified the cause of death on the far-away island. On being advised about the new conclusion after autopsy that death had resulted from thrombosis of the superior mesenteric vein, he deferred to the pathologist and issued another death certificate bearing the revised cause of death. As soon as the widow received this new certificate, she immediately brought suit against the government for malpractice, claiming that the treatment given, namely, gastric lavage, was highly improper for thrombosis of the superior mesenteric vein!

This case is an excellent illustration of how an incomplete autopsy performed in total disregard of the circumstances and clinical findings resulted in an entirely erroneous conclusion. The pathologist was unaware of and completely ignored the fact that there had been a prior identical episode of acute illness with coma and recovery and tacit admission by the deceased of having taken an overdose of barbiturates, and subsequent similar behavior and circum-

stances of coma a second time but with no response to the same treatment administered successfully the first time. The fact that the deceased had never suffered any abdominal pain and was in coma, hardly the symptoms one would expect if there had been a thrombosis of the superior mesenteric vein, and that there were no associated findings in the bowel or demonstrable primary cause for a thrombosis at autopsy, was totally disregarded by the pathologist. The erroneous conclusion was drawn solely on the basis of a clotted superior mesenteric vein in a well-embalmed body in which it is not at all unusual to find blood firmly clotted in large vessels as the result of contact with the concentrated formalin of embalming fluid. In this case it would have been better had no autopsy been performed than the incomplete one that was. Autopsies do not automatically provide the correct answer, contrary to the general impression.

Another somewhat comparable case may also be included to illustrate the same point. Again, the deceased was a middle-aged man who had been heavily addicted to alcohol and rehabilitated to a reasonable state of abstinence. One evening he attended a business and dinner meeting with a group of associates, and as sometimes happens, the occasion was a convivial one with considerable drinking. His associates bade him goodbye and allowed him to drive off alone in his automobile in the early morning. He lived in a suburb about twenty miles from the city but never arrived there. The road home was a wide one and ran parallel to but a fairly safe distance from a drainage ditch with a sloping side leading up to the level of the highway. At the break of dawn a bus driver traveling across a bridge over the ditch saw what appeared to be a car on the lower part of the inclined wall of the ditch with its front end submerged. He drove back to investigate and found the car without a driver. The front doors of the vehicle were partly submerged and the right rear door which was above the water level was open. The surface of the sloping bank of the ditch was damp and slippery. A prompt search was made for the driver in the water of the ditch. The deceased was found submerged and dead on the bottom at a depth of six feet. The body was identified as that of the missing driver. An elderly coroner of the county was called to the scene. Learning that the deceased had been drinking prior to starting for home, he concluded that he had lost his way in the dark and driven off the road down the side of the ditch. He reasonably deduced that the deceased had climbed back into the unsubmerged portion of the car and had gotten out through the right rear door and because of unsteadiness had probably slipped and fallen into the ditch and drowned. An autopsy at this time unfortunately was not carried out.

A certificate of death was issued accordingly and the body turned over to the undertaker, who took it to the city in the same county where it was promptly embalmed. Another member of the coroner's staff then assumed jurisdiction over the case and decided that an autopsy should be performed but totally disregarded the circumstances under which the body was found. The autopsy was described as revealing thrombosis of one of the coronary arteries. The condition of the artery was otherwise not described and no microscopic

examination of the occluded vessel was reported. Death was recertified as having resulted from coronary thrombosis and this certificate was placed on file.

The deceased carried an insurance policy which provided \$50,000 payment for death and an additional \$50,000, or double indemnity, in the event of accidental death. When an insurance claim was filed, the ordinary death benefit was promptly paid on the basis of a natural cause of death, namely, "coronary thrombosis." The widow beneficiary wondered why the accidental death benefits were not forthcoming and made inquiry to the insurance company. She was told by the company's home office in New York that the death certificate did not indicate an accidental cause of death but a natural one. She then complained to the local insurance company officials, who in turn transmitted her understandable dissatisfaction to the home office. Investigation then disclosed the unusual circumstances of the death which had not been suspected by the insurance claim department from the information recorded on the official death certificate. Needless to say, prompt payment was made of the accidental death benefits.

It was entirely possible in this case that the so-called coronary artery thrombosis was a post mortem phenomenon induced by the formalin in the embalming fluid. Such apparent thrombi are commonly encountered in embalmed bodies and require microscopic clarification. It was evident that the deceased was not disabled at the wheel of his car by a coronary thrombosis, for if that had been the case, he would not have been able to climb back and out of the vehicle through the right rear door. Finally, even if the deceased had had a fresh or recent coronary thrombosis which caused the accident to happen, he would not necessarily have succumbed to that disease since coronary thrombosis need not be fatal, whereas submersion in six feet of water can reasonably be construed as an irreversible situation. Whether or not alcoholic intoxication caused the deceased to have the accident was not material in this case for the reason that the double indemnity provision of the insurance contract was not voided by the co-existence of such intoxication. There are far too many autopsies with forensic implications that are not done at the right time or are performed merely as a quest for findings, in disregard of significant circumstances, with resultant erroneous conclusions. The misinterpretation of many forensic autopsies has and will continue to result in serious miscarriages of justice.

Reliable and thorough observations in forensic medicine and pathology and reasonable conclusions derived from them are of immediate importance to the community. When errors and omissions occur during the observation and deductive processes in hospital autopsies, the effect on the sum total of accumulated medical knowledge is small in contrast to the seriousness of such errors in forensic autopsies which are always of immediate and direct concern to the public, either as next of kin of the deceased or as members of the community. In this connection one can point to the importance of detecting subtle forms of traumatic injury and their fatal complications. Many such cases go un-

recognized either because the deaths are not investigated routinely or competently or completely. Such cases when unlabeled, as they often are when discovered and even when medically observed, may escape recognition because they are not considered in any of the categories of deaths requiring official investigation. When obscure and unlabeled unnatural deaths, or natural deaths of the type which are of concern to the public health are encountered in many jurisdictions they are not accepted for official inquiry because suicidal or homicidal violence is not obviously apparent or evident.

Most coroners do not have the authority to order an autopsy in traumatic deaths which are not the result of criminal or suicidal violence. Apparently natural deaths are usually not inquired into, a policy which is deplorable in that it totally disregards the basic principle in forensic medicine that an individual can be seriously or fatally injured without immediate disability and external signs of traumatic injury. This principle is violated on innumerable occasions. The many occasions in which unsuspected violence is demonstrated during the routine careful performance of a forensic autopsy in the Medical Examiner's Office should serve as a blunt reminder of the deplorable situation that exists in most jurisdictions in the country where there is no provision for the routine proper investigation of such cases. Even with a well-established, organized and efficiently functioning medical examiner's system, deaths by subtle traumatic injury, poisoning, abortion, suicide, homicide and accident may escape detection.

The discovery of conspicuous findings during the performance of an autopsy may indicate why death occurred, but not the relationship or lack of relationship of these findings. An autopsy may disclose multiple substantial findings which are obviously unrelated in a pathological sense, but without indication from the autopsy alone as to which of the unrelated findings is the cause of death. In some instances during a post mortem examination, a finding is revealed which, if correctly recognized and properly interpreted, permits an entire reconstruction of the fatal circumstances and leads to the discovery of an existing hazard. Again, there are many examples to illustrate these points.

There is the case of a man who was taken from his home to the hospital in coma. He survived eight days. The possibility of traumatic injury was considered but there were no findings to establish this possibility and when death occurred the case was properly reported to the medical examiner for routine investigation. Autopsy disclosed a conspicuous large hemorrhage in the substance of the left temporal lobe and acute purulent meningitis at the base of the brain. The brain hemorrhage did not appear in any way different from a natural one in the same region. A careful search for an aneurysm of the medial cerebral artery as a possible source did not reveal any. The hemorrhage and the meningitis could be two separate or related causes of death, but any considered connection could not be ascertained from the autopsy until subsequent information from a young lady who came to identify the body of the deceased provided the interesting and significant fact that she had seen and spoken to the deceased on the street two days prior to his hospital admission ten days

prior to his death. At that time she observed a surgical dressing over his left eye and on inquiry learned from him that he had been in an argument with his girl friend. He had evidently visited her for the purpose of taking back the many gifts he had given her when he was on friendly terms. When these were not forthcoming he smashed what he saw of them, including the television set. This occurrence, in conjunction with a beating, understandably aroused the young lady's anger. The patient told the witness that the girl had then picked up and struck him in the left upper eyelid with a small screw driver. He then went to the eye clinic where the wound was dressed.

The seriousness of the injury was not recognized because of the apparent lack of injury to the eyeball and of symptoms other than alcoholism. This incident happened on a Saturday. The man had been advised to return to the clinic on Monday but was unable to do so because coma had intervened and he was removed to the same hospital instead. The fact that he was the same patient who had been treated in the eye clinic remained unknown during his hospitalization. After this information about the deceased was obtained from this humble source, the left upper eyelid was scrutinized and revealed a very small completely healed scar in the medial portion of the tarsal fold that initially had not suggested a perforating puncture wound inflicted ten days before. There was slight injection of the bulbar conjunctiva but otherwise the anterior portion of the eye did not reveal any suggestive appearance. On removal of the eyeball, a faint tan discoloration of the periorbital fat was noted. On microscopic examination this disclosed a reparative reaction in the form of granulation, slight leukocytic infiltration and resorbing hemorrhage. The blade of the weapon, which was only two inches long, had evidently penetrated the superior orbital fissure in the posterior portion of the orbit without fracturing its bony margins, and had reached the fissure of Sylvius to damage the temporal pole of the brain and the blood vessels in the vicinity. This unsuspected homicidal penetrating wound was responsible for both the delayed acute cerebral hemorrhage and the acute purulent meningitis. The traumatic and common origin of these two fatal complications would not have been established were it not for the unsolicited information from the identifying witness without which this homicidal death would have gone unrecognized. It is important for the forensic pathologist to be on the alert for information from every source in puzzling cases.

In another case in which the deceased was a derelict and was found dead, autopsy disclosed an old healed tan-colored brain laceration with abundant adhesions of the scarred brain to the dura. There was evidence of chronic alcoholism in the form of a fatty liver. The heart disclosed extensive occlusive coronary arteriosclerosis, a condition not infrequently encountered in chronic alcoholics despite the common impression that occlusive coronary artery disease is not apt to occur in such persons.

Did death result from convulsive seizures induced by the old healed brain laceration or from occlusive coronary artery disease? The pathologist can only reveal the findings but cannot from the autopsy alone state the cause of death

without additional information as to prior symptoms and manner in which death occurred. Such cases are of more than theoretic interest, for if the old brain injury had resulted from an accident during employment, the relatives, that is to say, the widow, dependent children under eighteen years of age and dependent parents, would be entitled to benefits from the employer or his insurance carrier under the Workmen's Compensation Law. This would be true even though the deceased had abandoned his family and was no longer gainfully employed. If the deceased died of occlusive coronary artery disease, the death would be unrelated to any prior injury to the head. In such a case the autopsy findings revealed two possible causes of death which the pathologist could not arbitrarily determine without additional information.

There is the case in which the autopsy by the findings in a single organ reveals the cause of death and enables the medical examiner to reconstruct all of the preceding circumstances to disclose a continuing hazard responsible for the disability and death, and by expanding the investigation, discover similar unsuspected existing hazards.

Carbon monoxide poisoning provides such unlabeled situations in which the victim may be found in coma and brought to the hospital without suspicion of such poisoning having occurred. The victim may be suspected of having ingested poison as the cause of his coma, particularly if the family unintentionally supplies a misleading history of mental depression for which barbiturates had been prescribed. The hospital tentatively treats the patient for this condition. Neurological manifestations, however, are not suggestive of an overdose of barbiturates. Death may occur a day or two after admission without the true cause of death being recognized. Autopsy reveals bilateral symmetrical softening of the globus pallidus and extensive petechial hemorrhages in all parts of the white matter of the brain. The pathological picture is very striking and should be recognized promptly as having resulted from delayed acute carbon monoxide poisoning. One dreads to think of the delay in recognition when the brain in such an unsuspected case is removed and placed in fixative without being sectioned at the time. Many other poisonings from the same unsuspected source could result in the interim. In such cases the brain must be examined immediately and the findings recognized if proper measures are to be taken for the discovery and elimination of the hazard in the home or elsewhere responsible for the poisoning. In this instance carbon monoxide poisoning was immediately suspected from the characteristic appearance of the brain, and the presence of the petechial hemorrhages in the white matter suggested a relatively prolonged type of asphyxiation which could result only if the concentration of carbon monoxide in the air were in the order of 1,000 parts, or thereabouts, per million. These conditions are apt to be found when a gas flame refrigerator operates defectively and produces carbon monoxide by incomplete combustion. The fact that these refrigerators are not vented to the outside but discharge their products of incomplete combustion into the atmosphere of the room has been responsible for many serious and fatal cases of carbon monoxide poisoning. This is true regardless of the nature of the

fuel, whether manufactured gas with a high content of carbon monoxide to begin with, or natural gas or bottled gas which does not contain any carbon monoxide. The carbon monoxide in such cases is generated by incomplete combustion of fuel gas. The burner has a safety device to shut off the raw gas supply if the flame should be extinguished, but this only prevents explosions or poisoning by raw gas inhalation. The elaboration of carbon monoxide by incomplete combustion is peculiar to the fuel combustion in this type of apparatus. Such equipment may no longer be installed for domestic use in New York City. The manufacturing company is now exporting its product!

In the case just described, subsequent inspection of the premises where the deceased was found unconscious two days before her death disclosed the presence of a gas flame refrigerator still in operation and discharging 1,000 parts per million of carbon monoxide into the atmosphere of the apartment. A routine inspection of other apartments in the same building uncovered seventeen other similar defectively operating refrigerators, a source of a hazard which was immediately corrected.

In these last described instances, the observations were easily made but the correct interpretation of the obvious findings in the first instance was dependent upon information from a totally unsuspected source; in the second case the interpretations of the unrelated findings as to the proper selection of the cause of death was dependent upon reliable information from witnesses and prior history; in the last case the observations required recognition and then their solution and many ramifications could be predicted from the findings and needed only corroboration and prompt corrective action.

A series of varied fatalities which should be and usually are reported to the medical examiner has been presented in order to illustrate the importance of observation, recognition and proper and careful interpretation, and also to indicate in part what an official medicolegal agency is responsible for and should accomplish if it is to give adequate service to the community and to justice.

Some Comments on Observation in Medicine, in Literature, and in Life*

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Even in the Electronic and Orbital Age no one will contest the importance of observation in clinical medicine. The physician wants to perceive whatever confronts him and he wants to perceive it accurately, completely and rapidly. In urgent situations it is rapidity that must take precedence. In all other situations the emphasis is on accuracy. The degree of completeness to be sought will vary with the exigencies of the individual problem. There have been eminent clinicians who saw almost everything and there have been eminent clinicians who saw only what was important. Both types may stand at the summit of practical usefulness and both may contribute observations which lead beyond clinical diagnosis to clinical discovery.

Observation connotes the conscious recognition of a sensory impression. In common parlance we have sometimes debased the attribute "observant" by bestowing it on the routinist, the man who first hears the expected rale when a heart is failing or who first sees the jaundice in a case of colic. In a far higher category is the observer who notices the *unexpected* or the *unprecedented*.

I do not know who first recognized that the moon always presents nearly the same face to the earth and inferred from this that it rotates on its axis in the same time in which it accomplishes its revolution. Here we have a simple observation and a transcendental conclusion.

It is said that a monk, walking in his garden, noticed that in the earliest moments of the morning and the latest moments of the evening the color of the flowers was different from what it appeared to be during full daylight. This astounding observation is believed to have led ultimately to the discovery of the retinal rods and cones (1).

Dr. Arthur Fishberg's valuable book *Hypertension and Nephritis* tells us that old clinicians formerly tested for impairment of renal function by observing the absence of odor in urine after the patient had eaten asparagus (2). Whoever first observed this phenomenon possessed almost superhuman acuity, since he had noticed the *absence* of something, and negative observations seem to be the most elusive of all (3).

For twenty years I was exposed to talk about the white-centered petechiae which occur in subacute bacterial endocarditis. After two decades of this unobservant teaching and learning I read in the writings of Dieulafoy that the centers of petechiae are *chamois* colored (4). Immediately it became obvious that I had been working among amaurots.

Many first-class observations, like coins in a poorbox, were contributed by

* Dedicated to Professor Nathan Comfort Starr.

persons who can no longer be traced or can only be traced with difficulty. We would like to know who first noticed that in roentgen films of the chest the right lower lung field is more distinct than the left. Who first noticed that in scurvy the hairs are broken off short in the affected follicles? Who first noticed that the cutaneous eruptions of secondary syphilis may appear in the black parts of a two-color tattoo but not in the red? Who first recognized that in an outbreak of yellow fever the first cases occur in houses near the docks (5)?

The literature also contains some notable instances of observational failure. Perhaps the most famous is that of Claude Bernard. As Michael Foster says: "Indeed Bernard himself tells us that from the beginning of his experimental studies in 1841, he had repeatedly divided the cervical sympathetic without observing the phenomena which he saw for the first time in 1851. In these previous experiments his attention, like that of others, had been directed to the pupil; it was not until the day that he looked for changes in the face and ear that he saw them . . ." (6).

Another striking observational failure is mentioned by Cole: "It says much for the impetuous but barren industry of scholasticism that Spigelius, a well-known and reputable anatomist, should have produced in 1618 at the mature age of forty an entire memoir of some ninety pages on the tapeworm, without succeeding in discovering its head" (7).

We physicians sometimes forget that laymen have contributed many eye-opening and open-eyed medical observations. I shall here cite only one. The architect Benjamin G. B. Latrobe (1766-1820) spent the last twenty months of his life in New Orleans. His diary and sketchbook contain an astonishing collection of clinical, epidemiological and entomological observations on yellow fever (8), including a description of four kinds of mosquito, one of which is clearly *Aedes aegypti* (9). Latrobe's book reminds one of the Hippocratic dictum that the physician should not be reluctant to learn from laymen (10).

The presence of superior observations in many old writings inclines us to suppose that our predecessors were more observant than our contemporaries. I do not know that this can be proved. Indeed, the entire proposition is reminiscent of the battle between the ancients and the moderns, which so greatly exercised Sir William Temple and Jonathan Swift. The whole thing may be an artifact of history.

To begin with, there would seem to be no reliable method by which the acuteness of dead clinicians can be measured. Moreover, literature is an incomplete, eclectic and inaccurate record of life. We all know observant clinicians who have rarely written a line and we all have read authors whose sole possession was a pen.

It should also be said that the medical literature contains rhinestones among the diamonds. For example the eminent Albrecht Meckel published a case of aortic coarctation in which the ribs were said to be eroded at their *lower* borders (11). Another man recorded the statement that people afflicted with Malta fever did poorly on goats' milk.

All in all it would be rash to conclude that the older authors were sharper than the newer and we are probably unjustified in putting a halo around the past. Hippocrates said that bad physicians compose the great majority (12).

Another problem is the relation between observational acuity and intelligence. Since this question belongs in the domain of the psychologist, it would be unwise for others to intrude. But I cannot avoid mentioning the opinion, encountered from time to time, that acuity may exist apart from high intelligence. For example, a tradition is current to the effect that Richard Bright was a superior observer but an undistinguished thinker. Of counsel for the defence we have Sir William Hale-White, who wrote: "He was an extraordinary man. It is impossible to place geniuses in order, but he is certainly among the first five or six in medical profession. To him and to a few others an altogether marvellous power of observation has been given but Bright's genius took him further than mere observation, however brilliant, for he could correlate his observations . . ." (13).

From reading Bright's essays on kidney disease and on abdominal tumors I consider it unquestionable that Bright possessed synthetic powers such as few medical writers have ever manifested.

The relation between acuity and intelligence is discussed by Marcel Proust, a novelist who is famous for his microscopically detailed descriptions of human behavior and who, moreover, was much interested in physicians. Proust made the following remarkable comment: "A man may be illiterate, and make stupid puns, and yet have a special gift, which no amount of general culture can replace—such as the gift of a great strategist or physician. And so it was not merely as an obscure practitioner, who had attained in course of time to European celebrity, that the rest of his profession regarded Cottard. The most intelligent of the younger doctors used to assert . . . that if they themselves ever fell ill Cottard was the only one of the leading men to whom they would entrust their lives. No doubt they preferred, socially, to meet certain others who were better read, more artistic, with whom they could discuss Nietzsche and Wagner . . . Yet everybody praised the quickness, the penetration, the unerring confidence with which, at a glance, he could diagnose disease . . ." (14).

Opinions like this one of Proust's impress us deeply but we should not be overborne by them, since the question is one for the professional psychologist to settle if he can.

While it proves difficult to guess the relation between general intelligence—a vague entity—and observation, it is commonly accepted that observation is strongly influenced by the observer's knowledge, antecedent experience, and preconceptions. According to the old aphorism:

*We see what lies
Behind our eyes.*

A Frenchman whose book I can no longer find states that if someone shows you that a certain rock is shaped like the head of an elephant you can never again look at the rock without noticing the resemblance.

A good example of this kind of preconditioning is found in the poem "Grongar Hill" by John Dyer. It is impossible to read this short romantic description without recognizing that the author had been a painter.

Exactly analogous is the work of Laënnec. Whoever reads attentively the *Treatise on Mediate Auscultation* must perceive that Laënnec was a musician and that his musical gift helped him develop the art of auscultation (15).

In the same way a physician who has been trained in philology and literature is likely to notice his patient's speech, intonation, grammar and vocabulary, and from these he will rapidly draw conclusions as to the patient's origins, social condition and mental state (16). It by no means follows that the same physician will necessarily be more observant than his fellows with respect to other components of the clinical picture. And, to generalize the matter still further, it is by no means certain that immoderate accretions of knowledge are necessarily a boon to observation. We have always had men who learn from books and men who learn from life.

Passing from considerations of this character we must now turn to consider some of the circumstances which condition observation in clinical medicine. For reasons already given, I am unwilling to assert that the physicians of previous generations were, on the average, better observers than those of our time. But I am convinced that *interest* in physical diagnosis has declined, most especially as regards inspection and somewhat less in the case of palpation. Auscultation also has suffered a decline from which—as a kind friend has reminded me—it is perhaps being rescued by the new developments in cardiac surgery (17).

I think, but cannot prove, that we tend to be worst at inspection. Perhaps this deficiency is in some way a reflection of our national character, which embodies elements of haste, tension and overwork. Perhaps our urban upbringing helps stifle observation.

If you ride in a train, anywhere except in the scenic West, you will find that no one raises the windowblind above the midlevel at which the porter has set it. No passenger cares to look out.

As regards the realm of medical observation, there are specific unfavorable factors to which the physician is exposed. Some of these are: the noisiness of American cities, not excluding hospitals; the use of artificial light; and the fact that hospital beds are usually too high for the examiner.

I will risk the surmise that American elementary and secondary schooling, presently in a condition approaching gangrene, are in part responsible for our habitual inattention. Fingerprinting has ousted the old-fashioned drawing. The child is not encouraged to make a representational picture of anything; instead, he is asked to liberate his little psyche. This is perhaps beneficial but it is not conducive to the development of observation.

I do not know whether women are better observers than men. In any culture the daily routine activities of women are specialized. In our system the woman takes care of the home and the children and usually does most of the purchasing. Female clothing is much more elaborate and conspicuous than the clothing of men and is more varied in form and color. Further, women are

expected to be beautiful while maleness involves no such obligation. It follows then that our culture has imposed upon women a preoccupation with small and visible details, hence women often astonish us with accuracy of their observations. But they are far from infallible and I have known a young mother who had failed to notice that her child had jaundice.

In his premedical stages the future physician is exposed or overexposed to chemistry. It has been assumed that this subject develops the power of observation. I think we have too long deluded ourselves in this belief. The premedical student of chemistry follows a printed or mimeographed laboratory manual. When he adds sodium chloride to a solution of silver nitrate, he "observes" a precipitate. Then he must hurry on to the next procedure. Are we to believe that this type of standardized cookbookery adds an iota to anyone's powers of observation?

What can be done to help the medical student and intern develop into an observer? The responsibility belongs with the teacher of physiology, the teacher of pathology, the teachers of pharmacology and bacteriology and the teachers of the clinical subjects. Among the clinical teachers those should be selected who have *interest* and practical experience. In this important respect the great theoretician is apt to be less useful than the obscure practitioner.

The teacher, also, has the duty of directing his student to the great masters of the past. Among the best and also the most interesting are Trousseau, Graves, Dieulafoy, Hippocrates, Laënnec, Charcot, Broadbent, and Dupuytren. Much can be gained, also, from wide reading outside the field of medicine. Here the poets, the realistic novelists and the better writers of detective stories—especially Conan Doyle—can be used to afford pleasure combined with edification. Even the historian, the biographer and the essayist may help the seeing eye. Here is what Suetonius says of the death of Julius Caesar: "... Finally three common slaves put him on a litter and carried him home, *with one arm hanging down*" (18).

But it must be confessed that despite the best of training, despite iron persistence, golden opportunities and wide reading, we all overlook some things that we wish we had seen. Let us take consolation from the works of a great leader: "I call all gods to witness that I have often, on further examination, seen things I had completely missed before" (19).

ACKNOWLEDGMENT

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Observation of Behavior: Ecological Approaches

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Ecological and experimental methods of science can be differentiated with precision. Ecological methods have input only: there is one-way communication between them and the phenomena to which they are applied; they disclose things and events unchanged by the techniques used to observe them. In this sense, ecological methods reveal natural occurrences; they answer the question: What goes on here? Experimental methods have both input and feedback: there is a circular coupling between them and the phenomena with which they deal; what they discover are resultants of the conditions imposed by the investigator's observational methods. In this sense experimental methods exhibit contrived phenomena. Experiments answer the question: What goes on here, under these conditions? Galileo was an ecologist when he timed the oscillations of the lamp in the cathedral at Pisa; he was an experimentalist when he dropped the weights from the tower.

It should be noted that ecological approaches to scientific problems are not incomplete, or defective experimental approaches. On the contrary, they provide knowledge that the best experimentation cannot provide, because experimentation by arranging conditions according to the concerns of the experimenter destroys the very thing an ecological investigation seeks to determine. The importance to science of experimental methods is everywhere recognized, but it is perhaps less widely realized that the ecological side of science is essential too. From a purely scientific viewpoint it is important to determine how nature is arranged, *i.e.*, its taxonomy, and how it is distributed on every level without alteration of any kind, and this can only be accomplished by ecological methods. And for the applied sciences, information about the unaltered world is necessary before applications can be made. An engineer, for example, could not build a bridge without detailed information about the bridge site, and this information can be secured only by methods that do not destroy the site in the process of surveying it. Similarly, no physician would give a therapeutic injection to a patient without knowledge of the patient's tolerance for the drug. Such knowledge is equally important for the behavioral sciences: for a teacher making an assignment, for a judge passing a sentence, and for a physician prescribing a treatment regimen; each should know the psychological terrain upon which the assignment, the sentence, or the regimen is to be placed. But this information is seldom available. It is not available because the ecological side of the behavioral sciences is poorly developed. There are a number of reasons for this.

ECOLOGICAL METHODS: FUNDAMENTAL PROBLEMS

Ecological methods must contend with the same fundamental problems in all sciences, namely, 1) with the development of non-interfering methods of ob-

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serving, and recording, and analyzing the phenomena of the science, 2) with the identification and description of the natural entities or events of the science, and their relevant contexts or environments, and 3) with the incorporation of empirically observed ecological relationships into a unified system of concepts and theories. We shall consider each of these in connection with the problem of investigating behavior.

Non-interfering Methods of Observation and Analysis. In most sciences, non-interfering methods are difficult to devise, though much has been achieved in the older sciences by means, for example, of radiological, resonance, sonar, magnetic, photographic, and electrical techniques. There are a number of reasons why progress has been especially difficult in connection with behavior.

First, few phenomena are so sensitive to outside influences as is much behavior. The very process of observation, itself, can constitute an interference: an observer, a camera, or a microphone can radically alter a person's situation, as the distress over "bugged" juries, tapped telephone wires and other invasions of privacy demonstrate.

Secondly, behavior and its context usually involve multiple, simultaneous variables in complicated interrelationships. To include only a few of these in a record is as destructive of behavior as active intervention. The disturbing effects of inadequate sampling of subjects is well known, and the importance of situational representativeness has been stressed by Brunswik (1); in addition, however, for ecological purposes, behavior must be "observed" and described in its contemporaneous entirety.

A third barrier to making undistorted behavior records lies in the fact that behavior and its context present a moving target without a repetitive cycle. In other words, behavior has sequential as well as simultaneous complexity. Furthermore, temporally separated segments of behavior are not independent; the significance of an action often depends upon what has preceded or upon what follows. This is clearly illustrated by language behavior. Take, for example, the sentence by William James, "A mind is an object in a world of other objects." The word "mind" in this sentence has an undeterminate meaning if it is considered alone. This exemplifies the general fact that instantaneous, cross-sections of behavior are not intact behavior specimens; they are behavior fragments. Observational methods that ignore behavior's time dimension are as destructive of its naturally occurring properties as are the impositions of experiments. Laymen recognize this; they act as though they see their associates' behavior occurring in units with a fragile temporal extension. Men are generally careful not to interrupt each other, thereby implying that interruption will shatter and destroy a person's behavior. In the canons of social etiquette, to interrupt a person in the midst of a behavior unit means that an urgency exists which justified the destruction, or it means malicious motivation or insensitivity on the part of the interrupter. Children are taught to "wait until he is finished." Just as one does not step on another person's toes, eat another person's food, or wreck another person's toys, one does not destroy another person's behavior-in-progress. Here is a lesson in research methodology, as well as in social conduct.

Identification of Behavior Units. When one has obtained, by whatever method, an extended entire specimen of behavior, one is faced with the problem of units. What are its parts and pieces?

Innumerable behavior segments have been identified and described, encompassing such diverse phenomena as a brain wave, a maze-learning trial, and a seizure; a three-minute segment of behavior, an after-dinner speech, and an answer to a questionnaire item. The behavior continuum can be divided into an infinite number of parts. These countless parts are of two types so far as their origin along the time dimension is concerned.

One type may be appropriately called *behavior tesserae* after the pieces of glass or marble used in mosaic work. Tesserae are created or selected by the mosaic maker to fulfill his artistic aims. Similarly, behavior tesserae are fragments of behavior that are created or selected by the investigator in accordance with his scientific aims. They occur when there is feedback between the investigator and behavior. Behavior tesserae are produced by tests, experiments, questionnaires and interviews, *i.e.*, by all methods where an investigator requires a subject to engage in actions to suit the investigator's scientific purposes. Behavior tesserae are produced, too, by research methods which divide the behavior continuum at predetermined points. In these cases, the beginning and the end points of the selected parts are determined by the purposes of the investigator, and do not coincide, except by chance, with natural units. Maze-learning trials, three-minute behavior segments, and answers to questionnaire items are behavior tesserae.

The other type of segment of the behavior continuum may be designated *behavior units*. Behavior units occur without intervention by the investigator; they are the self-generated, inherent, *i.e.*, the natural parts of a person's ongoing behavior. The boundaries of behavior units fall at those points of the behavior continuum where changes take place independently of the operations of the investigator. Brain waves, seizures, and after-dinner speeches are examples of behavior units.

There are, at the present time, two grounds for identifying and classifying behavior units. One ground is their structural-dynamic characteristics, the other is their material-content properties. These two grounds are illustrated in the following specimen record.

Benjamin Benrod, age 6 years, suffered from cerebral palsy and resided at a school for disabled children. Ben spoke slowly and with difficulty. He wore a corset continuously in order to maintain upright posture, and was confined to a chair almost the entire waking day. Ben could not stand alone and crawled only poorly and with greatest effort as the record shows. The record was made in the physical therapy room of the school during Ben's regular treatment period that was scheduled at 1:30 P.M. The persons who appear in the record in addition to Ben are Tom Benray, the physical therapist; Marilyn and Olivia, aides; Saline, a teacher; Celestia, Otto, Verne, and Hilda, other pupils. This record was made by Dr. Phil Schoggen.

Being Placed on Floor

1:29 Tom Benray came over from working with Celestia to Ben.

As he did so, he said in a very cheerful, pleasant, yet businesslike way, "O.K., Brother Benrod."

Ben made no response that I could see.

Then Tom unstrapped Ben from his chair, picked him up and put him down on the floor.

Ben seemed to accept this as just what he had expected; he displayed no particular feeling about it.

Joking with Tom about
Shoe Laces

Noticing that Ben's shoelaces were unfastened, Tom commented gaily and in a slightly teasing way, "How come your shoelaces are all undone?"

Ben mumbled quite happily, "I didn't do it."

Tom replied in a gay, joking and nonchalant way, "Oh, I know, I know. You didn't do it. You *never* do it."

Then Ben said happily, really enjoying himself, "Elmer did it."

Tom laughed restrainedly and said knowingly, "Oh, Elmer did it, huh? Yeah, Elmer always does it."

Having Shoes Tied by Tom

Conversing with Tom

1:30 Tom continued working with Ben's shoelaces.

Benjamin talked gaily away to Tom but Tom seemed to be paying very little, if any, attention.

Since he was not looking at me it was impossible for me to understand what Ben said.

Apparently Tom didn't understand either, for at one point Tom said questioningly, "Huh?"

Ben mumbled something else still quite gaily.

1:31 Celestia came over and spoke to Tom and Tom replied to her question.

Benjamin made no response nor took any notice of this interaction.

Tom continued lacing Ben's shoes.

Then Benjamin said something else to Tom.

I didn't understand what it was but I believe it was just pleasant conversation.

Tom said somewhat more seriously but still in a pleasant way, "How far are you going to crawl today?"

Benjamin mumbled. I couldn't tell for sure whether he was responding to Tom's question or not.

1:32 Tom finished with Ben's shoes and said gaily, "There you go!"

Then Tom picked Benjamin up from the floor.

He stood him up for just a moment and then placed him on the floor on his hands and knees.

Tom had a little trouble getting Ben settled in this position.

He moved Ben's hands close together and straight out in front of him.

He moved Ben's legs so that he sat in a froglike position on the calves of his legs and his feet.

Listening to Olivia
and Tom

1:33 Olivia walked in from the occupational therapy room and made a few gay, happy, cheerful remarks about the fact that Ben was going to be six very soon.

Ben looked up at her but made no other response.

Then Tom said somewhat seriously, "Well, any little boy who's going to be six is going to have to learn to crawl."

With this Olivia and Tom walked to the far end of the room, a distance of nine or ten feet which was established as the goal for Ben's crawling.

Ben did not try to say anything in response to the comments by Tom and Olivia, but I'm sure he understood what they said.

He sat on his hands and knees, jerking somewhat rhythmically, wiggling slightly, apparently trying to keep his balance.

Ben continued to sit on his hands and knees in this froglike fashion and seemed to be trying to balance himself.

Olivia returned to the occupational therapy room without further comment and Tom began talking with Celestia.

But Ben paid no attention to them.

1:34 Ben continued sitting in this froglike position.

He continued balancing, wiggling slightly as though he might be trying to crawl, although it wasn't clear that this was what he was trying to do.

Responding to Tom's
Command

Tom looked over from where he was working with Celestia and said pleasantly, with no irritation or impatience, "Come on, Ben. Let's go."

Ben made no response.

He continued his rhythmical jerking and wiggling.

1:35 Ben's face assumed a very serious look.

He began jerking harder and wiggling more rhythmically as though he were trying earnestly to crawl.

Tom continued talking with Celestia.

Responding to Tom's Demand	<p>But Ben paid no attention to them at all.</p> <p>Then Tom looked over at Benjamin and said with more insistence in his voice, "Come on, Ben. Crawl. Lift those knees way up. Now, your left knee, then your right."</p> <p>Benjamin made no verbal response but it seemed that he tried a little harder, shifting his weight so that he could slip a knee a fraction of an inch forward.</p>
	<p>So far Ben had not moved more than one or two inches from where he began.</p>
Imitating Celestia	<p>1:36 Celestia, taking up Tom's previous comment, said, "O.K., Benny. One, two," meaning that Ben should move his legs in a steady, rhythmic fashion.</p>
	<p>Her comment was very pleasant and cheerful and was not a demand of any kind.</p>
	<p>Ben, as far as I could tell, made no response to Celestia's remark.</p>
	<p>He continued his efforts to crawl.</p>
	<p>Again Celestia said quite pleasantly, "Come on. One, two."</p>
Responding to Tom's Question	<p>This time Ben looked over at Celestia and mocked her saying, "One, two," imitating Celestia's tone of voice.</p>
	<p>Then Ben grunted and whined just a little and tried to push himself forward along the floor.</p>
	<p>1:37 Ben wiggled and bounced quite hard again.</p>
	<p>The next 11 minutes of the record describing Ben's efforts to crawl are omitted.</p>
	<p>1:48 At this point Ben had moved about six feet from the starting place.</p>
Responding to Tom's Question	<p>Tom, who was standing just behind Benjamin, said pleasantly, "Can you see yourself in the mirror?"</p>
	<p>Ben replied, "No," matter-of-factly.</p>
	<p>Tom said, "Well, turn so that you can," in a businesslike way.</p>
	<p>The mirror was directly in front of Benjamin at the north end of the room.</p>
	<p>It was about five feet away from him.</p>
Responding to Tom's Question	<p>1:49 Benjamin continued struggling.</p>
	<p>He made whimpering sounds as he struggled along.</p>
	<p>Tom, still standing behind him, said insistently, "All right. Let's go. Let's go. Keep moving."</p>
	<p>Ben continued bouncing and wiggling as he struggled along.</p>

He was roughly seven feet from his starting point.

Tom turned away from Ben and walked toward the south end of the room where Celestia was standing.

1:50 Apparently in response to Tom's leaving him, Ben began fussing a little more.

He made more and more noise until he was almost crying aloud.

He kept trying, however, bouncing on his haunches and pulling with his hands.

The more he tried, the louder he fussed.

1:51 Ben kept fussing and wiggling.

His efforts were in vain, however; he had made no progress since Tom went to the other end of the room.

Ben continued struggling.

1:52 He stopped, turned his head around and peered back at Tom at the opposite end of the room.

This was the first time since he started that Ben apparently was not trying to crawl.

Tom, who was just standing quietly with his arms folded, patted his foot on the floor with impatience, indicating that Ben should get busy.

Then Ben promptly turned around and began trying again very hard.

Again Ben whimpered very intensively, just on the verge of crying.

1:53 Ben wiggled and bounced.

Five minutes of the record are omitted.

1:58 Tom came to the north end of the room and moved the mirror out of the way.

Then Tom pointed with his toe to a line on the floor and said seriously, "All right, Ben, get up to this line and then I'll put you in your chair. Let's go, now."

This was said somewhat hopefully and with real promise in his voice.

1:59 Ben tried with renewed effort, it seemed.

He bounced, wiggled vigorously and cried with a little restraint.

Ben was extremely involved in this and his efforts had been continuous from the very beginning except for the one point mentioned.

He continued now, wiggling, fussing, and crying as he tried to reach the point which Tom designated.

Crawling

Looking at Tom

Getting to Goal Line

Crawling
Getting to Goal Line

Ignoring Olivia

Asking Tom If He
Is at Goal Line

Being Placed
in Chair

With all the exertion Ben began coughing a little.

As he coughed he relaxed his efforts somewhat.

The line to which Tom had pointed was about two feet away from Ben.

2:00 Saline Cutton stepped into the doorway between the physical therapy room and the classroom and made a very bitter comment about a little boy who insisted on acting like a baby, saying that she was so tired of it she'd like to throw him in the lake.

She was obviously talking about Benjamin.

Ben, however, made no response.

I'm not even sure that he heard her.

He continued his wiggling and bouncing, trying to get to the line.

Olivia and Hilda came slowly through, going from occupational therapy into the classroom.

As Olivia neared Benjamin, she jumped over him, put one foot on each side and came down very hard making quite a noise.

This she did in a very joking, good-natured way.

Benjamin made no response to this but kept trying earnestly to get to the line.

Olivia went on into the classroom.

Ben had managed by this time to cover about half the distance.

2:02 He reached his hand out as far as he could, pointed to the line and looked up questioningly at Tom.

Tom, who was standing just on the other side of the line, looked down and said, "No, no. Now cut that out. That's fudging. You've got to get all the way up to the line. You've got to get your arms across and get your knees almost up there, about halfway across."

This was said in a more kindly, explanatory way.

Benjamin resumed his struggling, wiggling and bouncing as he tried to reach the required goal.

After just a little more effort, Tom said, "O.K.," with finality.

Then Tom went to the other end of the room and brought Ben's chair back.

Ben relaxed visibly and just sat waiting quietly.

Tom rolled the chair up to Benjamin.

2:03 Tom picked Benjamin up and set him down rather forcefully in his chair.

Being Placed in Chair

Listening to Scolding by Tom

Then as Tom began strapping Ben in his chair, Tom gave Ben a lecture about what was going to happen tomorrow if Ben insisted on continuing with his fussing and crying while he was in physical therapy.

He told Ben that he just wasn't going to have any more of this whimpering and fussing and that if he came in tomorrow and started whimpering and fussing they would go to the bathroom and Ben knew what would happen then.

"Going to the bathroom" means a spanking.

He told Ben that he was just getting lazier and lazier and he was going to have to snap out of it.

Tom was quite critical and very serious.

There was no attempt to be good-natured or to gloss over the criticism.

It was straightforward and almost bitter.

Ben made no observable response to this lecture. I'm sure, however, that he understood everything Tom said.

Then Tom, having finished strapping Ben in the chair, took hold of the back of the chair and shoved Ben out of the room with haste and dispatch.

He rolled him quickly up the ramp and took him into the classroom where he left him.

This is a segment of behavior which, however, continued minutes, hours, and days, even years before and after the actions described. The question to be determined is whether it comprises one or several units of Ben's behavior continuum, or if it is a behavior tessera. The analyst of the record identified the behavior units which are marked along the record. These are structural-dynamic units which have been called *behavior episodes*. They have as a common feature that behavior is directed throughout the course of each episode toward a single end-state or goal; the nature of the goals and of the kinds of actions that occur within the episodes are not relevant to their identification. The definition of episodes, techniques for identifying them, and studies of their properties and frequency of occurrence are presented in a number of publications (2, 3, 4).

Material-content units are also present in this record; within the episodes Ben's behavior was by no means uniform; different "kinds of behavior" can be identified. During the long episode of crawling, for example, there were intervals when Ben sat on his haunches, when he bounced and struggled, when he fussed and whimpered, when he was silent. Each of these was a naturally occurring part of Ben's behavior, and therefore each constituted a kind of behavior unit, in this case identified by the material-content properties.

Concepts and Theories for Ecological Behavior Data. Some psychologists have been greatly concerned with fundamental, "natural" behavior units from

a theoretical viewpoint. Tolman, Murray, Lewin, Meunzinger, Newcomb, for example, give a prominent place to the definition of a unit of behavior structure. The units with which all of these writers deal are constructs defined within the framework of theories; or, in some cases, the unit is an axiom upon which a whole system is based. One finds that these writers illustrate behavior units, but that the taxonomy and distribution of behavior units are not presented by them as empirical problems for the sciences of behavior.

ECOLOGICAL METHODS: THE PRESENT SITUATION

It is understandable why psychology has not been zealously inclined toward ecological methods and behavior taxonomy in view of the problems they present. Some indication of the place of ecological methods in the behavior sciences is provided by the methods in common use. Tests, interviews, questionnaires, and experiments are dominant, and all of these methods are designed, precisely, to destroy the naturally occurring conditions of subjects' lives and to substitute for them new situations prescribed by the investigator. Wright (3) analyzed the methods used in a sample of 1409 studies of child and adolescent behavior published in the 68-year period 1890-1958 and found 110 "observational" studies in the sample, *i.e.*, studies resting "upon direct observation . . . of naturally occurring things and events" (p. 71). By no means were all of these ecological studies as defined here; nonetheless, Wright's survey provides evidence that non-experimental approaches to behavior are not absent. It is interesting to note that the frequency of observational studies is negatively related to the subjects' ages: of 643 studies on preschool children, 104 (16 per cent) were observational studies, while three of 430 studies of adolescents (0.7 per cent) used observational methods.

This state of affairs has a curious and significant consequence for psychology at the present time. There is but one word for all structural units of its phenomena; this word is, of course, *behavior*. Behavior designates everything from reflex activity to the course of empire. Psychology has its subdivisions, and they have names; but the subdivisions have, in general, a different relation to the structure of its material than is true of nonpsychological sciences. Thus, in biology, we find cytology, genetics, neurology, and endocrinology, for example, sciences that are defined in terms of structural units of biological material. The same is true in the physical sciences, where subdivisions varying from atomic physics to astronomy are concerned with different units of physical material. In psychology, however, except for "reflex" and perhaps for "personality," we lack words for different structural units of psychological phenomena. Our designation of the subdivisions of psychology rests upon partial, quality-like characteristics of behavior rather than upon its structural divisions. In Stevens' handbook, for example, there are chapters upon such topics as emotion, learning and retention, cognitive processes, work and motor performance, vision, audition, taste, smell, and vestibular functions (5). Each chapter splits off, so to speak, from complete structural units of behavior single aspects for special consideration. On the other hand, if we look at a physiological textbook we

find that a good share of the chapters refer to particular kinds of units with which physiologists deal: with the heart, the kidneys, the bones, and the skin, for example. As a matter of fact, both the physiological and the psychological chapters of Stevens' handbook center about units of anatomy, not units of behavior: the neuron, the synapse, the endocrine glands, the eye, the ear, etc.

It is an interesting question why psychology has not been concerned with the parts and pieces in which behavioral material comes, since it has devoted so much attention to the formation of perceptual units of the physical world. This neglect may be a result of the precocious growth of the science. Psychology almost completely skipped the descriptive phase which is emphasized in the early stages of most science; it had experimentalists and testers, it had its Wundt, its Ebbinghaus and its Binet before it had its Vesalius, its Linnaeus or its Cuvier; in fact psychology has not yet had its Vesalius. Psychology must be alone among the sciences in having almost nothing to say about the occurrence of its phenomena in nature. If one wants to know about the distribution among men of long and of short units of behavior, of anger outbursts, of happy periods, of frustrating experiences, for example, one certainly should not turn to the scientist of behavior; he knows little more about these matters than laymen. It is interesting to note, however, that some specialized behavior sciences have been concerned with the units of behavior; this is a central problem, for example, in the language sciences and in musicology.

Despite the meager use of ecological methods there has nonetheless been considerable reconnaissance of ecological problems. For, while the distinction between ecological and experimental methods can be made, in principle, actual scientific procedures cannot be so easily catalogued. The relative emphasis placed upon input and feedback varies greatly, so that there occurs, in fact, a continuum from pure ecological methods, with no feedback whatsoever, to highly precise experimental techniques in which both input and feedback are carefully controlled.

Among the quasi-ecological methods there are many kinds of interviews. There are interviews where the person interviewed is asked to report his opinions, attitudes, or knowledge, *i.e.*, to behave under conditions imposed by the interviewer. For example:

You've read articles claiming that cigarette smoking makes it more likely that a person will get lung cancer. What do you think?

This is, in essence, an experiment. But there are interviews that use the person, himself, or an associate, as an observer, in retrospect, *i.e.*, as a source of information about past behavior. Elicited, retrospective reports range from those in which an informant describes his own or another's behavior as it was in the immediate past or years before (*e.g.*, mothers' reports upon their own and their children's behavior); and they range from reports about very restricted aspects of behavior (*e.g.*, voting behavior) to very general behavior descriptions (*e.g.*, biography or autobiography).

Retrospective ecological data obtained by interview are necessarily used

widely in law courts, in securing medical case histories, and in personal counseling. Their deficiencies for these purposes are generally well known and efforts to verify the information they provide are continually made. Despite their limitations retrospective reports will always be used in these cases because other data are not available. However, as elected sources of scientific data, it is well to keep in mind the shortcomings of retrospective interview data. They are especially liable to observation and memory distortions, and to transmission errors. Take the case, for example, of a mother's report of how she dealt with her child and how he responded a day, a week, a month, a year, or five years earlier. In this case one deals 1) with observations made by an untrained, emotionally involved person; 2) with memory traces distorted to an unknown degree by forgetting, repression, and confabulation; and 3) with information altered in unknown ways within a transmission system that connects the report of the interviewee and the data on the page before the investigator. Here is one complete process:

- I. An untrained observer
 - (1) makes casual observation, and
 - (2) retains its traces in his memory for x years when he
 - (3) tells it to an
- II. interviewer, who
 - (4) writes it in his notes, and later
 - (5) dictates it to a
- III. recording machine, which
 - (6) transmits it to a
- IV. typist, who
 - (7) prepares a typescript for an
- V. editor, who
 - (8) edits the record and returns it to the
- VI. typist, who
 - (9) prepares a second typescript and gives it to a
- VII. coder, who
 - (10) codes the content of the record and passes it to a
- VIII. puncher, who
 - (11) punches the code onto cards and gives them to a
- IX. sorter, who
 - (12) prepares the distributions and delivers the data to the
- X. investigator, for
 - (13) final analysis and interpretation.

This is an extreme case, but often four, five, six, even nine different intermediaries and six, seven, eight, even twelve different transmission processes intervene between a fallible observation and the data available for final analysis. A zoologist who attempted to identify and analyze a specimen on the basis of a report from a field worker who obtained the description from a farmer who told from memory what he had seen two years previously would surely have reservations. When we use such behavior data are we also studying Abominable Snowmen? Or is the situation different?

In some cases the situation may, in fact, be different. These are cases where the reports of informants are intended to provide a general picture of the sub-

ject's personality characteristics, not details of his behavior. Indeed, it is sometimes difficult to determine if a retrospective investigation is an ecological study of behavior and its contexts or a study of personality. When significant correlations are obtained between mothers' reports of their own behavior vis-à-vis their children and the children's observed behavior at a later time, the mothers' reports have empirical predictive validity, even if the independent variable is not known: whether it is particular actions of the mother, her general personality traits, environmental conditions common to mothers and children, or genes common to mothers and children. Miller and Swanson discuss issues of this kind in connection with retrospective interview data (6).

Quasi-ecological techniques include many procedures for making samples of behavior observations. A common one involves tallying the occurrences of defined behavior attributes within observation periods of predetermined duration at predetermined times, *e.g.*, tallying the occurrence of the restless movements, or the aggressive acts of a subject during one, three, or five-minute periods of observation made at sixty-minute intervals. In another commonly used technique, narrative records of behavior are made during designated periods. These methods may be regarded as providing minimal ecological data; it has been pointed out, however, that they alter natural behavior in unknown ways by ignoring its temporal dimension and/or destroying its simultaneous complexity.

However, quasi-ecological methods are very often entirely adequate for the problems for which they are used. These can never be "pure" ecological problems, but not all legitimate and important ecological problems must involve the whole spectrum of behavior and its context (7).

The most adequate ecological data at the present time are provided by sound motion pictures (or television tapes) and by verbal narrative records made by trained observers. But even these methods are by no means perfect. Both a camera and an observer can be disrupting. This raises the technical problems of reducing observer interference and of making allowances for that which remains. Ways of reducing interference are to prepare for the observation 1) by explaining the purposes of the procedures to the subject, 2) by accustoming the subject to the procedures, 3) by training observers in non-interfering techniques and arranging cameras and their controls most appropriately and 4) by limiting observational procedures to situations where they are effective. From the earliest days of systematic use of observers and cameras for recording the behavior of children, it has been repeatedly demonstrated that these procedures will make children almost oblivious to observers and cameras.

Probably most important for future ecological work in educational and medical institutions is the development of ethical standards for the making and use of observational and photographic records and the fostering of their acceptance as routine procedures.

Photographic records have both shortcomings and advantages. The technical difficulties of photographic records are well known; more important for scientific ecological records are some other difficulties. For the understanding of

molar behavior and its context, more is often needed than the lens and film are able to record. Behavior always occurs with reference to only a portion of the multiplicity of things and events surrounding the person. This behavior-and-context forms a pattern, a figure, against the nonrelevant background, and it can be seen and described by an observer. The camera cannot be thus selective. Also, the behavior-and-context is often not limited to the immediately contiguous areas which is all that the camera sees; what is behind the camera and out of the limited range of its lens is lost. On the other hand, less is required than the camera records within the area where it operates; it provides much more detail than is needed for many problems, and the task remains, after the film is made, of selecting what is significant from the vast amount of material. The advantages of the filmed record lie in the preservation of molecular details which are lost in verbal accounts and the opportunity the film provides the investigator to go back and "look again"; these are crucial advantages for some investigations.

A verbal narrative has certain technical advantages as a system for recording individual behavior on the level of molar actions. Some of these advantages derive from a narrative's own characteristics as behavior: it is continuous, as behavior is continuous, and in this respect is isomorphic with the behavior continuum. Also, language has symbol systems for directed actions, and for representing single and multiple channels of action. The vast number of temporal, relational, and linking terms, and the vaster number of terms describing behavior attributes make language invaluable for recording the behavior. Literary language has been suspect as a tool for science, and the effort to achieve greater precision via formulae, graphs, numbers, meter readings, photographs, etc. continues. However, rich, descriptive language is at the present time the recording medium par excellence of the stream of behavior and it appears that it is likely to remain so. Not the least advantage of a narrative, a specimen record, is that it requires no special equipment or unusual technical skill. It does, however, require training to make good records, but medical personnel on many levels can learn to do this. The potential value of specimen records is suggested by the following record of a medical examination and conference involving 3½ year old Raymond Gibbons, his father, and Dr. Ellington. This specimen record was made by Louise Shedd Barker.

As we went into the doctor's office, the father carried Raymond and put him on the examining table.

The father said, "Boy, he has an awful time sleeping."

Dr. Ellington said, "Well, he's got an obstruction. You can see the adenoidal tissue that we call tonsils and you can see that they're swollen; but all the other adenoidal tissue that you can't see is also swollen, and he does have a hard time breathing."

The doctor said, "Open big now, come on boy, open big," as he put a tongue depressor between Raymond's teeth.

Raymond didn't open his mouth adequately, and his father urged him, "Come on, open up your mouth now."

Raymond responded to the command and the tongue depressor.

The doctor looked down his throat and said, "It's worse than ever."

Then he added, "He's had his primary immunization shots hasn't he, diphtheria, tetanus and all those?"

The father said, "Yes, he has."

And the doctor said, "It almost looks like a diphtheria throat."

The doctor continued, "You're not out of the Chloromycetin yet are you? You have some left?"

The father answered, "I think we have enough for today."

All during the examination and conference, Raymond was very active; he was wiggling on the table; later when he was off the table he was trying to get at things in spite of his father's effort to restrain him.

Then the doctor said, "This time I'm going to see him every time he runs out of medicine, even if it means seeing him every two or three days. If we were in a big teaching hospital we would put some of that throat scraping on Petri dishes and then we'd try out all the different drugs, that is all the antibiotics, and see which one would work. But in the country like this we have to work in the dark, sometimes. We have to do a certain amount of guessing.

"Now your wife has me really worried about this boy, and I'm doing just the best I can. You can see he's not toxic, he's not sick. But he does have this bad obstruction, however it's really no worse, in fact it will be hard to determine when it gets a little better."

The father mentioned the fact that Raymond has lots of phlegm that comes out of his nose.

Dr. Ellington ignored this comment and went on to say, "Of course, it might be a virus and then the antibiotics don't mean much, or it might be a staphylococcus which is resistant to the antibiotics. If the child seemed droopy and feverish instead of just a jack-in-the-box and active, I would think we ought to send him to the hospital now.

"Now," Dr. Ellington continued emphatically, "I'm going to write a prescription and this time I want him to take it every four hours. Do you know how often he takes his medicine now?"

Mr. Gibbons said, rather uncertainly, "I think every four hours."

Dr. Ellington said, "Sometimes I give it every six hours, but in this case, I want him to take it every four. His tonsils are just meeting at the midline and I don't know how he eats."

Mr. Gibbons said, "Well, he doesn't eat very much, he ate an egg at 1:30

this morning because that was what he wanted, but he doesn't eat a lot."

The doctor said, "That's home service for you; he wouldn't get that in a hospital. Give him as much liquid as you can."

Then Dr. Ellington said, "This time I'm going to do something I rarely do, as usually I like to consider the expense, but I want to see him every two or three days, every time when he is out of medicine."

"I think we can go back and see where we fouled up. When you first came in on the 27th, I gave a cheaper drug, one that isn't as potent as the one he has now, one that I sometimes use if I'm trying to save the people some money, and it just seemed to me as though you'd had one or the other of the children in about every other week."

"On January 2nd, I saw him again and gave him Chloromycetin, and on January 7th, he was reported as almost well and instead of seeing him as I should have I assumed the same thing would happen that happens with most children; that is, that nature would take over and that he would go on getting better."

"Instead of that he had this other flare-up and got much worse again. If he doesn't improve in these next three days we may send him to the University. It wouldn't do any good to send him to Longmont because they don't have the lab set up."

Then Dr. Ellington asked, "Is his breathing any better than it was the last time I saw him?"

Mr. Gibbons said, "Well, he breathes and sleeps better through the day and at night he seems to have most trouble; he'll sleep a little while and wake up and be all choked up."

Dr. Ellington said, "We all breathe better standing up, it's just the way our anatomy is made," and he touched his own chest as he spoke.

"One thing you can do is to raise the whole head of the bed, put the springs up on books or something. Not so far that he will slide down, but enough so that he is supported and stays up."

Raymond was in constant motion though his father kept restraining arms around him.

Again Dr. Ellington said, "He certainly doesn't act sick, he doesn't act the least bit droopy. You can't help but get excited when you look at that throat and see all that exudate, all pussy and scummy."

"But," he said, "we'll wait and see, most youngsters if you just get them over the hump then they'll go on the rest of the way; but that isn't the way it was with him."

Then Dr. Ellington again commenting on Raymond's behavior said, "He acts like somebody gave him," and mentioned by name a couple of stimulants, "is he like this all the time?"

Then he addressed the boy and said, "Slow down, boy, slow down, sit quiet, don't you know you're having trouble breathing?"

At this time Dr. Ellington handed the prescription to Mr. Gibbons and said, "Now take him home and put him in solitary."

Mr. Gibbons took the prescription, picked up Raymond as he said "Good-bye" to Dr. Ellington.

The aim of the physician is to understand the patient whole and in the fullness of his natural environment. Although procedures which dismantle the patient and describe his minutest parts in special, contrived situations are essential steps in this grand design, at some point it is necessary to make use of tender, sensitive non-interfering techniques for investigating the patient's larger systems, and finally the whole man. This is an ecological problem, and in the case of the whole man, behavior is the paramount phenomenon. Both medical research scientists and medical practitioners have an opportunity here. The incorporation into medical records of full descriptions of the behavior and living conditions of patients (in the consulting room, in the sick room of the hospital and at home, in the operating room, and in the treatment situation) can do much to disclose when communication between doctor and patient succeeds and when it fails, and to reveal why treatment regimens are sometimes carried through and why they sometimes miscarry. Furthermore, by bringing the great descriptive skills of medical experience to bear upon the behavioral side of illness, medicine can make an important contribution to the behavioral sciences. Medically trained men have made such contributions in the past. Here is another opportunity; the ecology of human behavior is in the beginning stages.

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Clinical Observation in Hippocrates: An Essay on the Evolution of the Diagnostic Art

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In 1804, the twelfth year of the French Revolution, René Théophile Hyacinthe Laënnec submitted to the Medical School of the University of Paris a doctoral dissertation titled "Propositions Concerning the Hippocratic Doctrine in Relation to Practical Medicine" (1). Despite the tremendous political and intellectual upheavals of this period, Laënnec, who was later to invent the stethoscope, was inspired by the medical writings of the Hippocratic corpus of the fourth century B.C., a collection which includes many writings composed by Hippocrates himself, as well as several contributions attributable to the school of Cnidos, and some which apparently had other origins.

The first proposition in Laënnec's thesis reads as follows:

"The only method of acquiring solid knowledge of medicine is in refusing principles not proven by a great number of specific facts, by a thorough study of the character and course of diseases and by the results of therapy based on observation of similar cases. Hippocrates said that this method was known long before his time and he considered it the only way to real discoveries" (2).

It is instructive to look back and see what the writings of Hippocrates contain that is valuable to us nowadays.

ANAMNESIS AND PHYSICAL EXAMINATION

Hippocrates felt that the taking of a patient's history by intelligent questioning was the first step to diagnosis. In the present era, when stereotyped history charts begin to replace the searching questions of the physician, his advice is especially timely:

"Leave nothing to chance, overlook nothing; combine contradictory observations and allow yourself enough time" (3).

Hippocrates stated that a lay person could possibly give an approximate description by careful compilation, but "much of what the physician should know besides, without the patient's telling him, would be omitted" (4).

His examination of the patient was probably more thorough than written case histories reveal:

"It is appropriate to submit the body of the patient to careful observation, using one's sight, ear, sense of taste, smell and touch, and the power of reasoning" (5). . . . "One should pay attention to the first day the patient felt weak; one should inquire why and when it began. These are the key points to keep in mind. After these questions have been cautiously considered, one should ask the patient how his head feels, if he has any pain or if he feels heavy. Then one should ex-

amine him for pain in the area below the diaphragm or in the pleura; if the muscles of the hypochondrium are tender or of normal tension; if the abdomen appears equal on both sides, or if it feels full. In regard to the chest, one should ask the patient if he has pain there and if he has a slight cough, with pain in the abdomen when he coughs. One should also ask the patient whether he feels a twist or pain in the bowel. When one of these symptoms arises, especially in the hypochondrium, one should evacuate the bowel with an enema . . . The physician should then ask whether the patient feels faint when getting up and can breathe easily. One should examine the stools to see if they are deep black or look normal. One should watch if the fever becomes acute on the third day.* In such cases examine the patient very carefully on the third day and look for other symptoms" (6).

The ancient writer also indicated a number of danger signals and other important signs which the physician should anticipate. He paid special attention to the type of respiration, to the evacuations, and to the patient's mental state. He carefully observed the hands, nostrils, and tongue and he looked for other signs too numerous to cite. He was confident that the physician would gradually accumulate enough experience to foretell the ultimate outcome of an illness and to be able to predict impending death many days in advance. The ancient physician refused, as a rule, to attend patients with a hopeless prognosis since he had no remedy to offer.

MILIEU EXTÉRIEUR

Many passages in the Hippocratic writings suggest that the review of the patient's history and the physical examination were not separate procedures as is the case nowadays. Ancient physicians paid close attention to the immediate surroundings of their patients, to their economic status (since only the rich had healthful accommodations), to local factors and to the patient's constitution. The latter was considered in its entire relation to the environmental factors since the Greeks assumed that body and soul reacted continuously to the surrounding world. Even disease was often regarded as an extraneous factor intruding into the body.

Our own approach to the patient runs the risk of inadequacy. We sometimes tend to neglect the consideration of external influences since technical advances apparently have somewhat reduced their effect.

Hippocrates wrote:

"In regard to the diagnosis of disease, we learn from the nature which we all share and from each person's individual disposition, from the sickness, and from the observations of the patient himself" (7).

The sum total of the external influences and the reaction of the body were called by Hippocrates the *katastasis*. This word was used in relation to the person, the disease itself and the environment. *Katastasis* is commonly translated "constitution." This leads the modern reader astray by suggesting the preponderance of hereditary factors in the make-up of the individual person.

* There was much malaria in ancient Greece.

However, the physicians of the seventeenth century, especially Thomas Sydenham, still followed the Hippocratic lead in considering the personal constitution of the patient, his diathesis, as the effect of external influences. It appears appropriate to choose a different word such as "condition" for the translation of *katastasis*.

In order to appreciate all these influences one should watch, as Hippocrates suggested, "to which diseases the entire body is mostly inclined" (8). He advised:

"Observe the celestial constellations; the nature of each country; diet; customs; the age of the patient; speech; manners; fashion; even his silence; his thoughts; if he sleeps or is suffering from lack of sleep; the contents and origin of his dreams; . . . one has to study all these signs and to analyze what they portend" (9).

Obviously, somatic and psychological factors were considered on an equal level with observations of the "*milieu extérieur*."

THE FOUR STAGES OF CLINICAL THOUGHT

The observations recorded in the corpus Hippocraticum are cast in the form of numerous aphorisms, case histories and general discussions. The Hippocratic approach was not in principle different from our own. It appears different only if one discusses the physiological doctrines separately from the clinical content. If we regard the evolution of the description of specific diseases as a historical process in its own right, we find a certain pattern in the advance of the diagnostic art. We then recognize that the concept of each disease tends to evolve according to the same rule during all periods of medical history, and even in our own time. This progress of clinical observation is rather independent of the changing fashions of physiological doctrines.

The development of clinical diagnosis proceeds in four stages. The first two are the discovery of symptoms and of syndromes. The third and fourth are the analysis of pathologic-anatomical findings and of the essential causes of a disease. In regard to the first two stages, the following books of the Hippocratic collection are of foremost interest: the seven books on "Epidemics," the four books on "Diseases," and the book on "Internal Diseases." The purpose of these books was mainly to describe the symptoms of the patient, the prognosis of his illness, and if possible, the syndrome, which can be defined as a frequently encountered combination of symptoms.

Temkin has pointed out the important fact that Hippocrates refrains from diagnostic conclusions: "Where everything suggests a name for a disease, we miss it. Where he presents a probable diagnosis we feel uncertain about it" (10). Laënnec had a somewhat different approach (11). He separated the symptoms essential to the diagnosis of a specific disease, "*les symptômes propres*," from those which may occur in any other illness, "*les signes communs*," or epiphenomena. Littré calls the common symptoms "*tableau général de la souffrance et des efforts des grands fonctions*." The common signs

represent a perfect guide to prognosis, whereas the understanding of the first group of observations, the specific signs, would depend to a great extent on the development of detailed anatomical and chemical knowledge. The ancient physicians aided by their astute observations were able to describe the epiphenomena in great detail. Their prognosis was based on the common signs, and these signs determined whether the patient was to be treated at all. Thus the common signs proved to be quite decisive for patient and physician alike.

These signs included a great number of important clinical observations and the record of the "*milieu extérieur*." By means of them the ancient physician tried to develop an exact prognosis, but he omitted from his writings most of the specific signs which would enable us to reconstruct a correct diagnosis from the old texts. Furthermore, very little was known of pathological changes and causative agents.

Hippocrates' famous book on "Prognosis" starts with the following words:

"I hold that it is an excellent thing for a physician to practice forecasting. For if he discover and declare unaided by the side of his patients the present, the past and the future, and fill in the gaps in the account given by the sick, he will be the more believed to understand the cases, so that men will confidently entrust themselves to him for treatment" (12).

On the question whether a patient should be treated at all, Hippocrates wrote:

"Medicine has enough reasons to justify its treatment, and why it would rightly refuse to take obstinate cases...as shown by the present essay (13)... For if a man demands from the art a power over what does not belong to the art... his ignorance is more allied to madness than to lack of knowledge" (14).

Laënnec's thesis does not explain completely why Hippocrates put so much emphasis on common signs and prognostic considerations. The present study of the Hippocratic writings will demonstrate that these books fit the pattern of the four successive stages of diagnostic thought which were mentioned previously. It appears only natural that the earlier stages of this development should be found more frequently in the ancient writings since attainment of the third and fourth stages required further accessions of knowledge.

The evolution of the diagnostic art usually proceeds in accordance with the following pattern, regardless of what disease we have in mind: first, the purely symptomatic description; second, the correlation of individual symptoms into groups outlining a syndrome; third, the discovery of anatomical changes typical of each syndrome; fourth, the discovery of the causative agent, be it a virus, bacterium or any other factor of biological, chemical or mechanical nature. But the succession of these four stages does not invariably or necessarily proceed in the order just outlined.

It would be wrong to assume that any one of the stages has been connected with a definite historical period. We can find examples of each stage in the Hippocratic writings. However, the bulk of the observations of the ancients belongs in the first and second diagnostic groups. Examples of complete under-

standing of the diagnostic problem are rare in the Hippocratic books. We find this accomplishment only in the orthopedic treatises; for this reason these surgical books appear to us so outstanding and of almost contemporary spirit.

In the following sections some of Hippocrates' clinical observations will be arranged and discussed according to this pattern of the four stages of diagnostic thought.

PROGNOSIS AND THE SYMPTOMATIC APPROACH

The Hippocratic books "Aphorisms," "Prognosis" and "Praenotiones Coacae" ("Predictions by the School of Cos") are probably the most frequently reprinted books of the entire Hippocratic collection and were quite popular until the early part of the last century. Until 150 years ago, medical diagnosis and therapeutics had not progressed greatly beyond the point reached in ancient times. To physicians who had hardly been able to advance beyond the first stages of clinical observation, the ancient collection of prognostic epigrams had great appeal. It supplemented their own limited experience and it enabled them to classify their observations into certain categories, especially since the Hippocratic aphorisms were already arranged in some kind of order. By comparing their own inadequate observations with the terse ancient sentences, these physicians were able to gain additional authority for their forecasts. They justified their own actions by referring to the time-honored experience of past generations of physicians. Only a few of the prognostic epigrams on acute and mostly febrile diseases, so often fatal, can be quoted here:

"It is a bad sign in all cases, when during high fever, the thirst subsides without obvious reason" (15).

"If the patients get startled when you touch them, they are in serious condition" (16).

"Sudden and successive changes from warm to cold in the extremities are ominous" (17).

"Livid spots appearing during fever herald immediate death" (18).

"Is a stuporous state always serious?" (19).

"Sleep which is deep but not disturbed definitely forecasts a crisis; but we cannot be sure of that when sleep is restless because of bodily pain" (20).

Francis Adams, the great Scottish country doctor, who a hundred years ago contributed so much to the understanding of ancient medicine by his beautiful translations, remarked that "the great superiority of the ancient savants over the modern was, that the former possessed a much greater talent for apprehending the general truth than the latter who confine their attention to particular facts, and neglect too much the observations of general appearances" (21). Adams meant, without referring to Laënnec, that it should always be possible to make a prognosis from the "*signes communs*," even if the "*symptômes propres*" are missing.

The detailed description of different types of respiration offers a fine example of these common signs. Hippocrates wrote:

"Frequent and small respiratory movements are the symptom of inflammation and pain in important organs. Deep respiration with great intermissions is a sign of delirium and convulsions. Cold breath is the sign of impending death. Fatal also is the hot and choking respiration.* But it is less serious than a cold breath.

Deep expiration with shallow inspiration or weak expiration with deep inspiration is also very serious and the sign of impending death. Equally serious is slow or very fast respiration, or a respiration faintly visible, or an inspiration with interruption, as if the patient would inhale twice. But a good respiration may turn the tide to recovery in all cases with acute fever if the patient has the crisis before the 40th day" (22).

Many, if not the majority, of the aphorisms in the prognostic books are hardly understandable to us. The ancient writer, for brevity's sake, referred mostly to single facts. In most instances his terse sentences connect one pertinent observation with the expected outcome of an illness, reminding us of the brief oracles of the priestess at Delphi. The prognostic anthologies offer a great contrast to the detailed and comprehensive observations which we find in Hippocrates' books on "Internal Diseases" and which represent the second, more advanced stage of clinical thought, the description of the syndrome.

These books, containing extensive clinical observations and more frequent reference to the affected organs, were probably influenced by the medical school of the Isle of Cnidos, south of Cos. The Cnidian physicians used to record more frequently than the school of Cos the "*symptômes propres*." They tried to determine which organ was the seat of illness. Hippocrates objected that they paid insufficient attention to the "*milieu extérieur*," to the general signs (23). He wrote: "They wanted to outline with exactitude the 'number' of each illness . . . and discover distinct diseases" (24). Hippocrates, considering this a fruitless enterprise, criticized the Cnidians for paying little attention to those signs which resulted from external influences and from which he tried to predict the future course of the disease: the weather, the seasons, the winds, the geographic location (25). Hippocrates wrote:

"Certain maladies or certain groups of people are more connected with a certain season, a certain location or certain habits (26). . . . The south wind makes hearing difficult, the eye dull, the head heavy; it makes one feel sluggish . . . During times of north wind, we observe cough, sore throat, constipation, dysuria with chills, pain in the chest . . . (27). . . . Every illness can occur in every season. But certain diseases have a predilection for a certain season, during which they start or become aggravated" (28).

Hippocrates thought that the system of his school emanated from the time-honored tradition of his own and earlier teachers at the Isle of Cos. From our point of view, the Cnidian concept was more advanced; it led to the discovery of the clinical syndrome.

We now understand that the approaches of Cnidos and of Cos were complementary. It is interesting to study the development of this controversy of clinical thought. It was a scholarly discussion between two ancient medical schools.

* The actual meaning of the latter word, *lignyodes*, is "smoky" in the sense of rich in CO₂.

In a footnote to his thesis, Laënnec wrote: "It is certainly a good thing to describe Hippocrates' system in our fashion. But to find out what he really thought is still better."

Before the discovery of modern nosology, the Cnidian books were less appreciated than the prognostic aphorisms from Cos. We moderns may have lost some perfection in the art of prognosis, but our gain in the art of diagnosis is beyond what Hippocrates himself ever could have anticipated. We feel closer to the school of Cnidos.

THE DISCOVERY OF THE SYNDROME

It is tempting to assume that the ancient case histories were written as lecture notes and were published, long after they were composed, by the Alexandrian school. It is perhaps for this reason that actual accounts of physical examination are missing. Moreover we know that members of ancient guilds requested that their techniques be kept secret and never committed to writing. Both schools of medicine followed this rule.

The alleged difference in the method of observation by the physicians of Cos and Cnidos was never consistent. We find some descriptions of localized diseases in those books which have definitely been attributed to Hippocrates himself and, on the other hand, remarks on external factors are encountered in the Cnidian books. The dogmatic difference between the schools of Cos and Cnidos was untenable in practice. But it is much more difficult to determine a diagnosis from case histories in the genuine Hippocratic books from Cos than from those of Cnidian origin.

Diseases such as tetanus, mumps, diphtheria, typhus and others were identified as syndromes long ago. In a previous paper I suggested (29) that case histories of yet unidentified diagnoses might correspond to cases of undulant fever, louse-borne Mediterranean relapsing fever, dengue, and a type of parotitis which is secondary to other infectious diseases. I also discussed the problem of epidemics of typhus. In the same paper I tried to explain that Hippocrates might also have observed a syndrome of splenomegaly with anemia in Egypt, and I suggested that this disease was probably schistosomiasis, which has always been endemic in the Nile valley. Hippocrates' description reminds us of the paper, originally published in 1894, in which Banti described cases of splenomegaly with anemia as a *syndrome* of unknown origin. Banti, like Hippocrates, was unable to advance his observations beyond this stage.

Most of the following case histories are from books influenced by the school of Cnidos. The physicians of this school even made attempts at differential diagnosis. A collection of diseases according to certain physiological systems, as for instance the respiratory tract or the alimentary canal, formed the basis for discussion of the differential diagnosis of these syndromes.

We will confine ourselves here to a discussion of respiratory diseases since a detailed analysis of one group of diseases will give us better insight into the

working methods of the ancient school than would a superficial survey of their entire range of clinical observations.

DISEASES OF THE THROAT

The following are observations of several patients with throat infections:

"Quinsy (dog-collar). There are fever, chills, headache; the region below the jaws is swollen; the patient, hardly able to swallow his saliva, spits it out as solidified little pieces. There is gurgling in the larynx. If you pull the tongue forward, you can see that the uvula is loose and not swollen, but the pharynx inside is full of hardened secretion, which the patient is unable to spit up. He cannot lie flat and if he did he would suffocate" (30).

In spite of the misleading title, one is justified in saying that this patient suffered from pseudomembranous tonsillitis or diphtheria.

The next case was possibly real quinsy:

"Bunch of Grapes. The uvula becomes swollen; mucus drips down in his head. The uvula hangs down low and turns red. If that lasts for a long time, the uvula may become black in the following manner: The large vein below the uvula becomes inflamed and from this inflammation it gets hot. Due to this heat, the uvula, attracting blood from the vein, turns dark. The patient will go into convulsions when you do not incise the uvula at the time of greatest swelling, because the blood of the overheated vein fills the surrounding tissue, suffocating the patient (31) . . ."

"Another Tonsillar Abscess. When the posterior part of the tongue and the glottis become inflamed, the patient is unable to swallow his saliva or anything else. . . . Suppuration sets in, mostly near the epiglottis. If it breaks open by itself, the patient will get well. Otherwise, feel with the finger whether it is soft. Then bind a sharp pointed blade to the finger and perforate the abscess. Thus the patient will recover since the disease is rarely fatal" (32).

Hippocrates described the difference between tonsillar abscess and phlegmon of the floor of the mouth, Ludwig's angina:

"Swelling under the tongue. If hypoglossitis sets in, the tongue and the entire area outside and below the tongue become edematous and feel hard to the touch. The patient is unable to swallow his saliva. . . . If it suppurates, one has to make an incision. Only rarely will it open spontaneously and subside without cutting. When it drains to the outside, one should cauterize" (33).

DISEASES OF THE CHEST: CORONARY INFARCTION AND PULMONARY EDEMA

The following case histories are taken from the third book of "Diseases." Interestingly enough, Littré's commentary on the first case to be quoted is: "Acute affection of the respiratory tract." But probably the case represents an account of acute coronary infarction with pulmonary edema. This description of myocardial infarction with acute cardiac decompensation is the earliest report of this disease I have found so far in the literature. It is easily overlooked because of the misleading Greek title: "The Lungs Swollen by Heat." Hippocrates wrote:

"When the lungs become filled by this heat and distended, a dry, hard cough will set in. The patient has to sit up (*orthopnoe*) and breathes fast and without pause. He gasps for breath (*asthmazei*) and sweats. His nostrils move like those of a racehorse. He sticks out his tongue frequently. A whistling sound comes from his chest and a heavy weight seems to lie on it. He cannot extend his chest, but feels as if it would burst. And great weakness overcomes him. A sharp pain grips him. He has the feeling as if needles were stuck in his back, chest and sides (*pleura*). He feels a burning as if he were sitting close to a fire. The skin on his back and chest may become flashing red. An intense gnawing pain overcomes him. He does not know whether he should stand, sit or lie down. Helplessly, he tosses around and believes that he is already dying. Mostly these cases die on the fourth or seventh day. Those who pass that day mostly survive" (34).

The restlessness is quite typical for acute coronary disease whereas the patient suffering from pleurisy mostly avoids violent motions. Hippocrates described pleurisy in entirely different words (see later).

This leads us to another observation in Hippocrates, that of the patient with pulmonary edema and transudate in the chest, who was apparently in an advanced state of cardiac decompensation. Hippocrates even recommended direct auscultation of the chest to confirm his diagnosis. He said:

"Dropsy of the lungs. Water accumulates; the patient has fever and cough; the respiration is fast; the feet become edematous; the nails appear curved and the patient suffers as if he had pus inside, only less severe and more protracted. . . . One can recognize that it is not pus but water. . . . If you put your ear against the chest you can hear it seethe inside like sour wine. . . . In some cases abdomen, scrotum and face swell up. . . ." (35).

In extreme cases, the physician was advised to incise the pleura at its lowest level to let the water out slowly by introducing some charpie. These patients usually died five to six days later with the symptoms of suppuration, cough and thirst. The cardiac etiology could hardly become evident to the ancient physician since pulmonary edema was frequently the ultimate stage of infectious and non-infectious diseases. Until the discovery of the circulation, passive pulmonary congestion was mostly considered a disease of the lungs.

ECHINOCOCCUS DISEASE

The following case history of hydatid cysts (echinococcus) gives us the impression that inspection of diseased organs was occasionally practiced by Hippocrates and greatly helpful for the differential diagnosis.

"Dropsy. Dropsy-originate also in the following manner: In summer, when one drinks much water at once, hydrops quite frequently sets in. . . . But it also can develop from tumors which grow in the chest, are filled with water and perforate into the thorax. I can prove this origin of hydrops by observations on cattle, dogs and pigs. These quadrupeds develop waterfilled tumors in the lungs. You can recognize that immediately: when you cut these tumors, water will pour forward. It appears that this occurs more frequently in man than in animals because of our unhealthy customs" (36).

The fluid in these cysts often appeared purulent. Obviously, a clinical differentiation between transudate, empyema and hydatid cysts was impossible, although an attempt at exact diagnosis was made. The parasitic origin of the disease was not even suspected.

Much space in these books was devoted to the surgical removal of the fluid. The technical procedure recommended was similar to that employed by us for the drainage of empyema as recently as thirty years ago.

PHTHISIS

Pulmonary tuberculosis was rampant and the description of "phthisis" is common in the Hippocratic books. The Greeks used the word *phthisis* for all wasting diseases ("phthino": waste away). But in some chapters the identification with pulmonary tuberculosis can hardly be questioned. Hippocrates outlined the classical picture: progressive emaciation, deep supra- and infraclavicular grooves; frequent cough with expectoration; prostration and long lasting fever; finally cachectic edema and death after about one year (37). In some case histories one cannot identify the disease which Hippocrates called phthisis. In many instances, we would consider cardiac failure complicated with angina pectoris or bronchiectasis (38). In other cases Hippocrates very clearly outlined even the constitutional features of patients already stricken or inclined to pulmonary tuberculosis. This picture is still familiar to those physicians who had the opportunity to see a good number of patients with pulmonary tuberculosis before the advent of chemotherapy. Hippocrates wrote:

"The physical characteristics of the consumptives were: smooth skin, pale and freckled; flushed appearance; bright eyes; slight edema; the shoulder blades projecting like wings [i.e. status asthenicus]. This is the same in women.... They are melancholic and hot blooded..." (39).

It is difficult to find many observations of the physical features of the patients as detailed as this in ancient medical writings. Hippocrates mostly characterized his patients in terms of the humoral doctrine, omitting the characteristic traits so significant to us.

PNEUMONIA

Many chapters of the Hippocratic collection deal with observations of cases of pleurisy, bronchiectasis, or abscesses of lungs or thorax. The word "empyema" can frequently be found in translations, due to a misunderstanding. The Greek word "*empyos*" should never be translated as "empyema" because it only implies "pus inside." The reader has to decide from the context whether these are cases of pulmonary abscess, bronchiectasis or empyema in the strict modern sense of the words.

We also often find the word "peripneumonia" in the original Greek text. This expression literally means a "disease concerning the lungs." However, the diagnosis of pneumonia should never be made from such titles but only after careful analysis of the description of each case.

Yet certain case histories definitely suggest the diagnosis of pneumonia. Hippocrates spoke of patients in whom "the upper lobe of the lungs is drawn tight" (40), or "the lungs are filled up" (41), or "a disease of the lungs" (42) has set in. In these cases, he wrote, pain was observed rarely, but when it occurred it could resemble the type of pain encountered in pleurisy. Sputum is common, gradually changing in consistency and color, from light and foamy to thick, yellow and bloody. Hippocrates even spoke of a crisis on the seventh day: "Most patients die on the seventh day. When they pass that critical day, they will not die" (43). This is quite typical of lobar pneumonia.

BRONCHIECTASIS

Hippocrates, of course could not diagnose, correctly and in our sense, cases of lobar pneumonia or bronchopneumonia. He also was always afraid that after the acute respiratory infection suppuration might set in. It is difficult for us to interpret his case histories, but one gains the impression that some of these chronically ill patients suffered from febrile bronchiectasis and that others had pulmonary abscess.

He described some instances of protracted fever in which, at the end of the second week after onset, the sputum became more copious and purulent. Subsequently the sputum became sweet, malodorous and finally putrid. He considered the chance of survival better when the offending matter was expectorated before the twenty-second day (44). Some patients apparently were ill for a long time, suffering from chronic cough. Expectoration was most copious in the early morning hours; this is typical of bronchiectasis. He wrote:

"There is another disease of the lungs when the patient coughs up a thick, yellowish and sweetish sputum; he shivers, has pain in the chest and back; there is a slight whistling in the larynx; the throat becomes parched; the eyelids red, the voice heavy, the feet swell up; the nails are curved; the upper part of the body becomes thin and the patient loses weight. The sputum has a nauseating taste when it gets into his mouth. He coughs mostly in the morning hours and after midnight, but also at other times" (45).

This description is suggestive of infected bronchiectasis.

PLEURISY AND PULMONARY ABSCESS

Pleurisy was considered closely related to pulmonary diseases although not every pain in the chest was regarded as a symptom of pleurisy. Hippocrates differentiated between three types, hemorrhagic, bilious ("serous, yellow") and the dry type of pleurisy without sputum. "One should suspect dry pleurisy when the pain is high up in the chest" (46). The description of dry pleurisy is unmistakable:

"When the lungs touch the pleura the patient will have cough, whitish sputum and orthopnoea. He feels pain in the chest and over the entire back. When recumbent, he feels pressure, thinking that he carries a weight in his chest. He feels a sharp pain like that of needles. We can hear a loud crepitation like that of old leather. The respiration is impaired. The patient can lie only on the af-

feeted side, not on the other. He holds the afflicted area with his hands while lying down . . . and feels as if a heavy weight is suspended inside his ribs. He almost imagines that he is breathing through the wall of his chest" (47).

In this chapter on chest diseases this is the second instance of direct auscultation by ancient physicians. Whether or not they also listened to the breath sounds is not known.

Hippocrates was able to give quite a logical account of his observations without the aid of autopsies. However, many chapters on internal diseases remain unclear. Some case histories try to explain what we would consider as empyema or pulmonary abscess. For example:

"One dies of pleurisy when from the beginning much mucus and bile collect in the pleura, and when much other matter flows in from other parts of the body, or if the patient cannot get rid of this phlegm by expectoration or resorption [literally, by dissolving it]" (48).

The following two observations by Hippocrates point out the presence of pulmonary abscess.

"The patient expectorates, at first, slightly purulent material; occasionally the sputum is dark and bloody. As time progresses, it draws together and becomes foul . . . and causes intense pain and fever; severe and frequent attacks of cough occur. Finally, the sputum turns into real pus. The fever will rise in the whole body, but especially in the affected area if this pus remains in the cavity (49). . . . But if the ripened pus breaks through and is expectorated completely, then the cavity in which the pus has been will collapse, secretion will dry up, and the patient will recover fully" (50).

Otherwise the prognosis would be very serious.

Hippocrates also stated that one should wait until an apparent pulmonary abscess perforates into the pleural cavity. This event gives temporary relief from the respiratory distress. He recommended that the physician wait for two weeks before applying the same method as recommended for drainage of empyema: incision with a knife or hot iron and drawing the pus to the outside by the introduction of fine linen threads. The exact location for the incision was to be determined by direct auscultation of the thorax while an attendant gently shook the chest of the patient. This is still called "succussio Hippocratis" (51).

Hippocrates outlined the different causes for such accumulation of pus in the chest:

"Those who accumulate pus (*empyos*) in the lungs have it from the following causes: Suppuration will set in if a patient suffering from disease of the lungs (*peripneumonia*) does not expectorate on the critical days and if the mucous secretions remain in the lungs" (52).

"Suppuration (*empyos*) also will occur if the mucus runs down from the head [*i.e.*, from the sinuses] into the lungs. In the beginning such dripping may remain unnoticed . . . Gradually fever will set in. . . (53) The lungs will also suppurate (*empyos*) in the following manner: when a little blood vessel ruptures because of strain, blood will escape according to the size of this vessel. . . . Part of this blood will be coughed up. But if the vessel does not close at once, blood

will find its way into the lungs, where it suppurates. Later, the patient will expectorate real pus, or blood tinged with pus or even red blood" (54).

The fourth cause of pulmonary suppuration is trauma, as Hippocrates explained in detail:

"Suppuration can also originate from great stress, from physical exercises or when something should rupture inside the chest, in front or back. The torn tissues will attract fluid if the patient does not expectorate the blood instantly or if, not being aware of his predicament from the beginning, he does nothing about it" (55).

The last cause of thoracic suppuration in the Hippocratic account is penetration of the chest wall and lungs by swords, daggers and arrows. For reasons of space the details of the interesting text will not be quoted here (56).

Up to this point in the present analysis only the diseases of the respiratory tract have been discussed. Since it is not feasible to reproduce more of the countless clinical observations which Hippocrates recorded, the examples already given must suffice to explain his method of diagnosis.

Hippocrates interpreted his observations in the terms of the doctrine of humors. Therefore we must attempt to ascertain whether this doctrine was also based on observation and whether a logical connection existed between the ancient system of diagnosis and the humoral doctrine.

EMPIRICAL ORIGIN OF THE DOCTRINE OF THE HUMORS

Hippocrates did not accept the doctrine of the four humors simply as an analogy to the concept of the four elements postulated by contemporary philosophers. Instead, he tried to confirm it by observation. Hippocrates said very clearly that he did not approve of analyzing diseases only according to preconceived assumptions. He could not explain the great variety of clinical observations by assuming the prevalence of one or other humor (57). However, he was obliged to use the current terminology as a system of classification for recording his observations. The following personal experience demonstrated to me the possible *empirical* background of the ancient humoral doctrine.

I was called to see an old man of Mediterranean origin who was suffering from an acute febrile illness. He vomited gastric secretions colored by reflux of yellow bile; he passed a dark watery discharge from his bowels; he expectorated massive amounts of tenacious sputum. He appeared to be a plethoric, heavy set man of ruddy complexion. His high blood pressure and vomiting had caused a considerable nosebleed. This patient represents a clinical demonstration of disturbance of all four humors if we are willing to describe a case of virus infection in ancient terms: vomiting as elimination of an excess of yellow bile; the watery bowel movements as a flow of black bile; phlegm pouring from his nostrils and bronchial tubes as mucous discharge; and finally the nosebleed. The ancient physicians would have treated him with syrups for the phlegm, with diet for the loose bowels and vomiting, and with bloodletting for nosebleed and plethora. The cause of the disease being unknown, these symptomatic procedures appeared perfectly logical.

In countless case histories Hippocrates described in a similar way and in great detail the relief of symptoms by evacuations of the humors. He frequently attempted to explain the "common signs" by referring to the accumulation of one or other humor. He found for instance, "yellow bile" in the pleuritic exudate; he assumed that thin pus was derived from decomposed mucus (phlegm) or blood. But flesh was considered as the source of thick and dark yellow pus. The doctrine of the four humors implied that the different constituents of the body could separate under the influence of illness, just as in the process of making cheese the milk becomes separated into its basic constituents, curd, whey and fat.

The outbreak of diseases often seemed to be caused by sudden atmospheric changes. At least, the ancients drew this conclusion from their observations of winds, seasons, rains and other environmental influences. These presumably caused imbalance of the humors. This observation of the "*milieu extérieur*," applied to the clinical picture, formed the basis for the understanding of many diseases. These hypothetical ideas about the causes of diseases took the place of the still undiscovered knowledge of the influence of biological and chemical agents.

Hippocrates was convinced that the elimination of an excess of humors would cause relief from illness. For this reason he constantly watched the effect of environmental conditions on the patient. He wrote:

"In regard to the influence of atmospheric conditions which have to be considered here, the following four observations will be helpful [*i.e.*, during an epidemic fever]: epistaxis; abundant flow of urine with a large sediment...; the flow of bile...; and loose bowels... Not in all patients do we judge the illness from one sign alone" (58).

Observations of such signs also formed a basis for his prognoses.

HIPPOCRATES' DEFINITION OF DISEASES

The ancient physicians often considered the separate symptoms as individual diseases. A single disease, in our sense, was frequently diagnosed as a combination of two or more diseases. When a number of common signs was observed at the same time, the illness appeared to be more dangerous. The patient discussed above would have been regarded as suffering from a combination of three diseases: dysentery, fever and bronchitis. Fever itself was regarded as an independent entity.

Since Hippocrates thought that diseased humors tend to accumulate where they already abound, he defined diseases usually according to such hypothetical disturbances (59). But, he warned "Do not demand names for any disease which we have, by chance, indicated in this book. For it is by the *symptoms* in all cases that you will know a disease that may come to a crisis" (60). For this reason, all names given to diseases in antiquity or added by later copyists, remained purely descriptive. A specific etiological and pathological nomenclature is the exclusive merit of modern medicine. However, it is wrong to regard Hippocrates' approach to the problem of clinical diagnosis as basically different

from ours. Hippocrates only remained confined to the first and second stage of diagnostic understanding. When he recognized and described a syndrome, he could not analyze it further for concomitant pathological or etiological factors. In spite of these difficulties he remained consistent when explaining different diseases.

We can define a *symptom* as "a phenomenon constituting a departure from a normal bodily condition or function" (61). Hippocrates had no other choice than to explain disease tentatively by assuming a disturbed balance of the humors. Furthermore, by definition "a *syndrome* constitutes a number of symptoms occurring together or a combination of symptoms in a disease" (62). This definition does not imply knowledge based on further research. Some authors of the Hippocratic collection described many diseases by combining symptoms that were frequently encountered in association. To syndromes of this kind Hippocrates justifiably applied such labels as "Dropsy of the Lungs," or "Dog Throat" or "Suppuration in the Chest." Many of these expressions related his clinical observations to the four humors or to popular names. Examples of such syndromes have been discussed above. In all these instances, Hippocrates was unable to proceed beyond the second stage of diagnostic understanding. However, the books on fractures and dislocations show a further advance of diagnostic acumen and do not involve us in speculative explanation by the humoral doctrine.

ORTHOPEDIC OBSERVATIONS

In Hippocrates' books on "Fractures" and "Diseases of the Joints," the mechanical cause of the illness was obvious in most instances. Logical diagnosis could be established by coordination of clinical and anatomical observations. Structural changes were easier to observe than in internal diseases. In many chapters of these books, Hippocrates accomplished the four stages of diagnostic thought which have been already discussed. Because of this, the modern reader immediately feels much more familiar with the mode of thinking of the ancient writer than he does when reading any other part of the Hippocratic collection.

The great chapters on orthopedic diseases fill at least one-fifth of the entire Hippocratic corpus, which comprises about 1300 large printed pages. Only a few outstanding examples can be quoted. We read in the chapter on the dislocation of the shoulder joint:

"As to the shoulder joint, I know only one dislocation, that into the armpit. I have never observed either the upward or outward form.... Practitioners indeed think that forward dislocation often happens, and they are especially deceived in cases where there is wasting of the flesh about the joint and arm; for in all such, the head of the humerus has an obvious projection forward... Suppose one laid bare the point of the shoulder of the fleshy parts from the arm and so denuded it at the part where the muscle is attached, and laid bare the tendon stretching along the armpit and collarbone to the chest; the head of the humerus would be seen to have a strongly marked projection forward, though not dislocated. For the head of the humerus is naturally inclined forward, while the

rest of the bone is curved outward. The humerus, when extended along the ribs, meets the cavity of the shoulder blade obliquely, but when the whole arm is extended to the front, then the head of the humerus comes in line with the cavity of the shoulder blade, and no longer appears to project forward" (63).

This quotation represents only a small part of the extensive treatise on diseases of the joints. It conveys the exactness and love of detail which characterize the entire book. Hippocrates analyzed different methods for reduction of the humerus and recommended the use of cautery in order to secure the surrounding tissue tightly about the head of the humerus.

In other chapters Hippocrates discussed the symptoms of avulsion of the acromion and its differential diagnosis from dislocation of the shoulder (64). He also described fractures of the clavicle. "Treatment is easier if the bone is broken straight across. But if it is fractured obliquely, treatment is more difficult" (65). Different types of treatment of other dislocations and fractures are discussed in great detail.

The chapter on "dislocation of the wrist" seems to be misinterpreted in all translations. The ancient text suggests a dislocation. There is no chapter in Hippocrates referring to fracture of the forearm (Colles' fracture). One can safely assume that this rather common fracture was consistently misunderstood by Hippocrates because Colles' fracture of the forearm often looks very much like dislocation of the wrist. The treatment suggested by Hippocrates is rather typical for reduction of this fracture, even by modern technique (66).

GIBBUS: TRAUMATIC AND TUBERCULOUS

The chapter on curvature of the spine and fractures of the vertebral column is outstanding. We read:

"When humpback occurs in children before the body has completed its growth, the legs and arms attain full size, but the body will not grow correspondingly at the spine. . . . Where the hump is above the diaphragm, the ribs do not enlarge in breadth, but forward, and the chest becomes pointed. . . . instead of broad; the patients also get short of breath and hoarse, for the cavities which receive and send out the breath have smaller capacity. Besides, they are also obliged to hold the neck concave at the great vertebra [*i.e.*, the seventh cervical vertebra], and the head may not be thrown forward. . . . In consequence of this attitude, such persons seem to have the larynx more projecting than the healthy. They also have, as a rule, hard and unripened little tumors in the lungs; for the origin of the curvature and contraction is in most cases due to such gatherings. . . . Cases where the curvature is below the diaphragm are sometimes complicated with affections of the kidneys and parts about the bladder, and besides there are purulent abscessions in the lumbar region and about the groins, chronic and hard to cure. . . . Many patients, too, have borne curvature well and with good health up to old age. . . . But few even of these survive sixty years. . . . There are some in whom the vertebrae are curved laterally to one side or the other. But these will be discussed among chronic diseases of the lung" (67).

These quotations are only small fragments of the extensive writings of Hippocrates on kyphoscoliosis. A more convincing description of vertebral

tuberculosis with involvement of the lungs and kidneys, complicated by psoas abscess, can hardly be found. Hippocrates also discussed the consequences of fractures and forcible dislocations of vertebrae:

"The spinal cord, too, would suffer, if the luxation due to jerking out of the vertebra had made so sharp a curve. The vertebra in springing out would press on the cord, even if it did not break it. . . . The cord then, being compressed and intercepted, would produce complete insensibility of many large and important parts, the physician would not have to trouble about how to adjust the vertebra. . . . One might do this with a corpse, but hardly with a living patient (68). . . . Curvature of the spine occurs even in healthy persons in many ways . . . and besides there is a giving way in old age . . ." (69).

Space does not allow further reference to other important chapters on fracture and dislocation or to such topics as injuries of the hand and their treatment. Large chapters are also devoted to diseases of the female organs.

Many of these books have been translated into English, French and German, and some are available in inexpensive editions. Details can be found in the bibliography.

THE METHOD OF HIPPOCRATES

Any physician who studies the writings of Hippocrates cannot escape the conclusion that the method of diagnosis employed by the ancient school was fundamentally the same as ours. Apparently this was also the opinion of Laënnec. We read in the handwritten marginalia to his dissertation:

"The method of Hippocrates or his manner of proceeding in the study of medicine: His method is simple and sure; it always has been used by all great minds, by all those who did not give false preference either to abstract thinking or to observation, but who used all their abilities in order to arrive at the discovery of the truth" (70).

Hippocratic medicine was symptomatic and based on "expectant observation," as Claude Bernard pointed out (71). Modern clinical medicine is founded on experiment. Equally, the ancient empirical therapy has made room for the modern therapy based on experiment and physiological research. However, modern clinical research still is based on the foundation laid down by Hippocrates and his successors.

If it is still necessary to assert the usefulness of studying ancient medical texts, we can refer to the following statement by Hippocrates:

"I declare, however, that we ought not to reject the ancient art as non-existent, or on the ground that its method of inquiry is faulty, just because it has not attained exactness in every detail, but much rather, because it has been able by reasoning to rise from deep ignorance to approximately perfect accuracy, I think we ought to admire the discoveries as the work, not of chance, but of inquiry rightly and correctly conducted" (72).

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Observations on Discogenic Sciatica

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The discogenic sciatic syndrome has continued to represent one of the most difficult and frustrating of the problems which confront the orthopedic surgeon. Once considered a self-limited ailment of the aged, sciatica now appears to be more frequent. It is most common in the middle-aged groups of thirty-five to fifty-five and is certainly no stranger to youths of high school and college age.

While sciatic pain is usually discogenic, it can reflect a wide variety of other lesions. Diagnosis is seldom simple. Careful and comprehensive study of each individual patient is required for accuracy and for the application of appropriate therapy. The present study summarizes current knowledge about sciatica in general and discogenic sciatica in particular, and discusses areas in which knowledge is sparse. The author offers his opinion concerning the interpretation of the individual findings and their importance in planning the treatment of the individual patient.

MECHANISMS OF SCIATIC PAIN

The word "sciatica" implies neither a precise ailment nor a precise distribution of pain. Sciatic pain can result from at least three separate mechanisms:

Mechanism I. Direct pressure upon the nerve roots of the lumbar spine. It is difficult to understand why pressure on the nerve root causes pain since, at operation, pressure on the undamaged nerve root or even its section produces little discomfort. It has been supposed that the root must be engorged or inflamed for pain to result (1). However, the prompt relief that can follow the surgical removal of herniated material is convincing evidence of the relationship of nerve root pressure to pain. Among the many causes of sciatica of this type may be mentioned abscess, cyst or neoplasm of the cauda equina, spondylolisthesis and, of course, pressure of the herniated disc.

Mechanism II. A deep irritative lesion of any character located in or adjacent to a low lumbar or upper sacral dermatome. In a beautifully simple series of experiments, Lewis and Kellgren (2, 3) demonstrated the patterns of radiation from such lesions by the injection of small quantities of hypertonic saline solution. Such injections into the deep structures about the pelvis subperiosteally, into the vertebral laminae, and into the intervertebral spinal ligaments of the area, consistently produced radiation of pain in the involved dermatome. When local pain was severe, radiation from adjacent dermatomes was added. This mechanism is clinically responsible for the type of sciatic

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pain accompanying irritated or inflammatory lesions of lumbar lymph nodes, pyelitis, ureteral calculus, etc. The author questions the belief of some gynecologists that malposition of the uterus or fibromas can cause sciatica, unless the tumors are as large as the uterus of late pregnancy. Irritative lesions of the low lumbar vertebrae, sacrum, ilium and even the hip joints are not uncommon causes of pain radiating down the leg. By the same mechanism, the degenerated disc itself may produce referred sciatic pain in the total absence of pressure on the nerve roots as has been frequently demonstrated by negative myelography or surgical exploration. Lesions which cause sciatic pain in the absence of root pressure produce no clear neurological findings. The converse is not always the case. Pain due to root pressure may occur in the total absence of positive neurological signs.

Mechanism III. A third mechanism is sometimes responsible for sciatic pain: *direct pressure upon the pain fibers of the spinal cord—even at high dorsal levels.* Although rare, instances of sciatica as the only presenting symptom of dorsal cord tumor have appeared repeatedly in the literature. In the young patient, demyelination of the cord fibers occasionally appears to account for sciatica as the initial complaint in multiple sclerosis.

PATTERNS OF RADIATION

Although each of these mechanisms causes pain to radiate into the leg, their radiation patterns cannot be called precise or consistent.

Radiation from root pressure may involve more than a single root or partial pressure upon one or upon several roots. Moreover, there are common variations in root distribution and in the skeletal construction of the lumbar spine. Dermatome radiation also often varies from the pattern that might be anticipated anatomically. Overlapping of adjacent dermatomes varies the radiation pattern. Moreover dermatomal radiation has the curious property that it may result in pain limited to small sections of the anticipated area. The author has frequently encountered examples of such pains limited to the toes, the metatarsal area, the outer border of the foot, the instep, the heel, or the lateral calf. Such areas have been subjected to extensive local therapy and even to surgical operation under the erroneous impression that a concealed local lesion was responsible. It is not surprising that the sciatic pain caused by pressure upon the dorsal spinal cord likewise follows no typical or characteristic pattern.

THE DISC

Although a wide range of lesions operating through these mechanisms may produce sciatic pain, in most instances sciatica has been shown to emanate from lesions involving one or more of the low lumbar discs. The disc is a complex structure that has been the subject of intensive study since the original reports of herniation by Schmorl and his pupils (4 to 7) and especially since the demonstration of herniation as the cause of sciatica by Mixter and Barr (8) in 1934. Although our knowledge of the mechanism and behavior of the

disc is still far from adequate, a brief survey of present knowledge is necessary for the interpretation of the clinical picture of the individual patient. The outstanding contributions of Friberg, Hirsch, and their colleagues (9 to 14) of the Karolinska Institute of Stockholm have added greatly to our knowledge of the growth and of the pathological and clinical behavior of the disc. Their observations will be drawn upon freely in this brief review.

DEVELOPMENT AND SIGNS OF AGING OF THE DISC

The disc is composed of a central nucleus surrounded by a firm laminar annulus of fibrous tissue in which elastic fibers have been observed (7). Originally central, the nucleus moves posteriorly during growth. In adult life its tissue, originally gelatinous in consistency and of separate identity, is gradually encroached upon by the fibrous tissue from the annulus. As aging progresses, it shrinks as its fluid content diminishes and it becomes somewhat pulpy in consistency. The surrounding annulus is broad and strong anteriorly and laterally but is thin posteriorly because of the backward migration of the nucleus. It is weakest posterolaterally where it is not reinforced by the posterior longitudinal ligament which underlies the dura centrally. Microscopically, the fibers of the annulus are arranged concentrically to contain the nucleus, which serves as a ball-bearing axis for intervertebral motion and as a shock absorber. Originally, blood vessels enter the disc from the cancellous bone of adjacent vertebrae centrally. In adult life the entire structure is devoid of blood supply, nutrition being maintained by absorption from adjacent vertebral surfaces. Signs of aging can appear in the annulus as early as the age of fifteen. The normal fibrous structure tends to disappear. Fragmentation and zones of degeneration appear microscopically and gradually increase in frequency with the years (14). Later these zones may evolve into concentric "cracks" or cavities. Since these changes, like those of the nucleus, may be observed in all discs of the spinal column, they cannot be identified with sciatica and must be regarded as the physiological result of aging.

PATHOLOGICAL CHANGES IN THE ANNULUS

More meaningful in reference to low back symptoms are the changes in the disc which cannot be considered physiological and which occur mainly in the low cervical and low lumbar regions. As a result of the study of more than five hundred discs grossly and microscopically examined, Hirsch and Schajowicz noted the frequency of radial rents or tears which started centrally and extended sometimes posteriorly but mainly posterolaterally. These tears or rents were observed in between 20 to 35 per cent of the spines studied between the ages of thirty-five and fifty and were largely confined to the lumbar region, mainly involving the discs of the third, fourth and fifth lumbar interspaces. The tears, starting centrally sometimes as early as the age of fifteen, were of variable extent but were frequently complete, extending through the periphery of the structure (Fig. 1).

Occasional evidences of healing were noted, such as scars and ingrowth of



FIG. 1. The posterolateral rent in the annulus. Illustration from Hirsch and Schajowicz.

vascular granulation tissue emanating from the neighboring longitudinal ligament. The occurrence of these radial tears, chiefly in the low back and mostly coincident with the age group mainly affected by low backache, point to their having pathological rather than physiological significance. These radial tears either result from or provide a path for posterolateral bulging or extrusion

of the nucleus. Nuclear bulging results not only in loss of resistance of the disc to superimposed weight but also destroys its function as the axis of intervertebral motion. The gradual demand upon the annulus increases as nuclear function diminishes and with time, it sags, tends to spread and to tear further as the adjacent vertebral bodies approach each other. Sometimes when this occurs, pseudospondylolisthesis may appear on the radiograph (Figs. 2 A, 2B). When the tear is complete, disc material may be extruded and press upon the nerve root. In any event, the loss of controlled intervertebral motion



FIG. 2A. Longstanding lumbosacral disc disruption with beginning osteoarthritic changes.

FIG. 2B. Pseudospondylolisthesis at fourth interspace indicating a later disruption at this level. (Same patient ten years later.)

may result in laxity and instability of the joint and ultimately secondary osteoarthritic changes affecting the facets and adjacent vertebral borders.

That these changes may produce backache and sciatica is clear. Hirsch has demonstrated that, in the person who suffers from sciatica, the injection of pantopaque under pressure into the disrupted disc can produce severe exacerbation of back and sciatic pain. This does not occur when such injection is made into the normal disc. The mechanism by which these changes in the disc result in backache and dermatome radiation is obscure, since the disc appears to possess no nerve tissue. In fact, such lesions are often noted on lateral radiographs of patients who have never suffered backache or sciatica. In any event,

it is clear that the disc can cause sciatic pain by virtue of direct nerve root pressure (Mechanism I) or by virtue of dermatome radiation in association with severe backache (Mechanism II).

That similar objective disc changes and even herniation may exist in the total absence of either past or present backache or sciatica and that a violent attack of discogenic sciatica may be followed by complete spontaneous recovery continue without adequate explanation. Hirsch and Schajowicz (14) and Lindblom (12) suggest that pain fibers may be carried into the disrupted area with the ingrowth of vascular granulation tissue. Probably a simpler explanation is more valid. Radial tears interrupt the integrity of the concentric annular fibers. Accordingly, in response to the pressure of weight bearing and sudden extra demand, the disc may tend to spread and impinge upon the vascular posterior ligament, which is richly supplied with nerve endings. The posterolateral rent, gradually increasing, would appear to account for the frequency with which discogenic sciatica is so often preceded by recurrent or constant backache. However, the picture is not quite so simple as this might suggest. Efforts to produce disc rupture in normal fresh autopsy specimens by axial compression have been consistently unsuccessful though sufficient force was used to fracture adjoining vertebral bodies. It is most probable, therefore, that the initial vulnerability or disruption of the disc usually long antedates the appearance of symptoms and that the latter reflect further extension of the lesion. What then, is the cause of the initial lesion?

1. Without much doubt, there is a congenital factor. Similar lesions are encountered with almost equal frequency in the low cervical area, also just above the site where the architecture and function of the spinal column alters (10, 11). Moreover, disc lesions are often found directly above sites of skeletal asymmetry or malformation involving the fifth lumbar vertebrae or sacrum (Fig. 3).

2. In certain individuals, there would appear to be a diffuse biochemical fault in the discs causing them to give way and narrow prematurely and diffusely (Fig. 4). This phenomenon however, provides no clue to the selectivity that characterizes the usual low lumbar disc lesion.

3. A further causative possibility concerns the question of whether ligamentous structures and the avascular discs in particular are capable of strengthening in response to demand as do other skeletal structures. Frequent laboratory and clinical studies have clearly demonstrated improvement in muscle strength and endurance in response to carefully graded and regularly performed exercises. Similarly, in accordance with Wolff's Law, bone strengthens where demand upon it is greatest. No equivalent studies upon the response of ligaments to extra demand have been noted in the literature. Perhaps during adolescence or early adult life, current civilization may impose the stress of grueling contact sports with inadequate preparation, the initial lesion occurring silently at that time.

4. The interest of the author has been directed toward still another possible source of vulnerability of the low lumbar discs. As stated above, the backward

migration of the nucleus results in relative thinning of the posterior annulus. In the lateral radiograph of adolescents, it is usually possible to identify the location of the nucleus by depressions in the adjacent vertebral borders above and below (Figs. 5A, 5B). In the lateral radiographs of certain children suffering from occasional low backache, the author has observed excessive backward migration. A case in point is illustrated in Figure 5C, of the spine of a



FIG. 3. Disc disruption overlying the site of hemisacralization—a fairly frequent occurrence.

twelve year old girl who complained of mild interval backache associated with pain and paresthesia in the lateral aspect of the left leg.

Comparing this film with several examples taken at similar ages in the course of routine survey, the excessively posterior position of the nuclear depressions are apparent not only at the tender fourth interspace but also in the adjacent levels above. Figure 5D represents evidence of similar excessive nuclear migration at the fifth interspace.

Since the flexed rather than the extended spine is conducive to posterior

displacement of the nucleus, and since the normal lordosis is obliterated or reversed in the seated infant, it would seem possible that excessive migration can revert to the condition found at that early period. The not uncommon and widespread practice of bolstering the infant in the seated position too early and too long before sitting is assumed voluntarily is well known. Further



FIG. 4. Diffuse disc narrowing producing mild intermittent symptoms. Lesion suggestive of biochemical disturbance.

study of this possibility might prove rewarding in explaining vulnerability of the disc in at least a certain proportion of cases.

THE CLINICAL PICTURE

Precipitating Causes of Sciatica

The comprehensive studies of Hult (10, 11) upon over eleven hundred workers show clearly the important role of repeated trauma in producing sciatica, which was noted almost twice as frequently in heavy workers (11%) as in nonmanual workers (6.4%). A true accident was held responsible for



FIG. 5A and B. Lateral radiograph of the lumbar spines of adolescents taken to exclude skeletal trauma illustrative of usual placement of nuclear depressions.

the sciatic attack in 43.9% of the cases. This coincides closely with personal clinical experience. In many of the nontraumatic cases, one cannot fail to be impressed by the ever present equation between the aging and stiffening spine and the attempt to continue with youthful chores. Hult's studies failed to disclose an increased proportion of discogenic symptoms in workers whose pelvis were tilted because of inequality in the length of the legs or in those who had moderate degrees of kyphosis, scoliosis or other postural asymmetry such as lordosis, or obesity of moderate degree. This also coincides closely with the experience of the author, who has repeatedly noted the surprising freedom from back and sciatic symptoms among patients with enormous obesity and postural distortion and its not infrequent occurrence in persons who are markedly underweight. However, certain types of extra demand do seem to be clearly conducive to backache and sciatica. The fused hip and also stiffness or ankylosis in overlying regions of the spine would seem to cause sufficient extra demand upon the low back and to produce symptoms with frequency although probably only when antecedent disc deterioration has occurred. The asymmetric disc pressure of severe scoliosis in the lumbar area seems sufficient to produce initial and constantly increasing disc disruption and root pain (Fig. 6).

The Course of Sciatica

It has been stated that although the relationship of disc disruption to the back-sciatic syndrome is clear, disruption of the disc does not necessarily coincide with symptoms. Disrupted discs may remain totally silent and clinical experience reveals a good chance of spontaneous total recovery from discogenic sciatica even though the disruption is irreversible. Probably the most extensive recent study of conservative therapy was made by Soderberg (13), who undertook to investigate the subsequent course of three hundred and ten patients originally hospitalized for severe sciatica with neurological signs between the years of 1930 and 1945. The essential ingredient of the conservative therapy was bed rest. All except four patients were personally examined by him as late as twelve to eighteen years after hospitalization, and information about their condition was obtained at four years, eight years, and twelve years after the acute attack. Ten of these three hundred and ten patients were operated on after the initial hospitalization and were excluded from the survey, which concerned conservative treatment only. The detailed findings of this study may be sought in the original article; the essentials can be summarized as follows:

Fig. 5C. Lateral radiograph of child of twelve complaining of mild recurrent low backache and pain and paresthesia of the left lateral calf following competitive sport. Note excessive posterior migration at the fourth lumbar interspace (probably also at second and third interspaces). Nuclear depressions at fifth interspace are normal.

Fig. 5D. Asymptomatic but excessive posterior migration at lumbosacral level.

Average period of hospitalization	one to two months	
Average duration of symptoms	five to seven months	
Outcome eight years after hospitalization	entirely symptom-free	45.7%
	occasional mild pain	24%
	constant pain	13%
	recurrence	7.3%
	rather constant pain	10%



FIG. 6. The effect of severe localized scoliosis upon the disc.

A second examination of these patients twelve years after hospitalization revealed 51.7% to be entirely well. In this surgically minded era, there is a tendency to underestimate the frequency of spontaneous recovery from symptoms despite the apparently irreversible nature of their cause. Probably intervertebral stability may be achieved through the development of firm scar tissue or by the subsidence of engorgement and inflammatory swelling. The factor of nerve root pressure may be more readily accounted for. An extruded mass may gradually diminish in size either by absorption of exudate or by absorption of the herniated disc itself by granulation tissue issuing from the

posterior ligament. Moreover, the nerve can stretch, flatten or move to accommodate the herniated material.

THE SURVEY OF THE INDIVIDUAL PATIENT

The comprehensive survey of the sciatica sufferer must encompass the following:

1. *The acquisition of insight into the psychological make-up of the patient.* Like headache, backache and sciatica are essentially subjective complaints and lend themselves easily and frequently to gross exaggeration. Some insight into whether the latter is present and whether it is referable to malingering to evade service, for compensation or legal purposes, or due to some psychological disturbance, may be acquired if the patient is put at ease during the interview or if the findings are not consistent with the degree of somatic disturbance. In our Department of Orthopedic Surgery ward patients hospitalized with sciatica have the great advantage of discussing their problems with the psychiatrist of the Orthopedic Department; his evaluations have been of great help. Unfortunately, private patients do not accede easily to this type of consultation.

2. *The question of nondiscogenic factors.* On physical examination, superficial evidences of neurofibromatosis may be found. A tuft of hair over the sacrum can reflect underlying skeletal malformation, which should be studied radiographically. Suspicion of retroperitoneal lesions, mentioned above, may be supported by the finding of tenderness or masses on examination of the abdomen, flanks and costovertebral angles. Radiographs should be checked for the presence of ureteral calculus.

Skeletal lesions in the iliac flares may be difficult to detect on radiography because of overlying gas (Fig. 7) and may require repeated examinations. Bony metastases in the lumbar vertebrae or pelvis may cause severe pain before becoming detectable on the radiograph. Light percussion over the suspicious area may suggest their presence and constitute grounds for further study. Percussion tenderness when present is an extremely valuable aid in detecting occult neoplasms, infection, severe bone rarefaction, fracture and cauda equina neoplasm. Fracture and severe osteoporosis became apparent on radiography as do metastases of sufficient size.

3. *The disc.* Directing the study of the patient to the most frequent offenders, the low lumbar interspaces, the history of the patient must carefully review his daily tasks, with special reference to prolonged standing and jolting in trains, heavy lifting while bending forward or stooping (daily multiple bed making, gardening, laying of carpets, excessive calisthenics, etc.). In the patient of middle age, private practice reveals that regular chores or vigorous low back calisthenics are almost as often responsible for the acute attack as sudden trauma. The number of patients who disassociate vigorous morning aerobatics from resultant sciatic symptoms is surprising. The jolts and tumbles suffered by commuting straphangers constitute a common source of symptoms. The history of preceding back pain or sciatica or both, the duration,

frequency of attacks, their past response to treatment, and the type of treatment employed may be of great help in the planning of subsequent therapeutic measures. The distribution of pain should be elicited from the patient as accurately as possible as well as the presence of paresthesias. The patient afflicted with severe sciatica stands and walks with his back held in the more comfortable position of forward flexion. The normal lordosis is flattened or



FIG. 7. Lesion of left iliac flare difficult to identify because of overlying gas bubbles.

reversed, the erector spinae muscles are spastic, and the spine is listed toward the side opposite to the pain. The list of discogenic pain may be sufficiently marked to resemble true scoliosis but it contains no rotary component and it subsides on recumbency. The presence of local low back tenderness and the positive Lasegue test strongly indicate involvement of low lumbar discs. When positive, the Lasegue test serves as a reliable indication of subsequent improvement or retrogression if the angle made by the leg with the trunk is recorded. If the sciatica is mild or spotty, however, none of these findings may present. Sometimes the Lasegue test may reproduce sciatic pain at the

normal limit of straight leg raising. Occasionally, because of the abeyance of direct confirmatory findings, it may be necessary to resort to the therapeutic test of low back support, sometimes the results are surprising and gratifying. In dancers or vigorous calisthenic addicts, the Lasegue test can be negative despite severe sciatic agony. Palpation of the spinous processes may reveal a "step," which in association with the appearance of a shortened trunk, is suggestive of true spondylolisthesis.

4. *The neurological picture.* Primarily, the neurological examination must attempt to distinguish tumor of the cauda equina or cord from discogenic retropulsion. Although this differential is of the greatest clinical importance, it is especially difficult and not always possible. Instances of central retropulsion causing diffuse pressure on the cauda equina pose the greatest problem. Some 5 per cent of explorations for disc herniation reveal neoplasm instead (15). Bizarre sensory or motor findings, saddle area hypesthesia or anesthesia suggest prompt referral for neurological consultation. Although actual pressure of retropulsed material upon the nerve root or roots cannot be assumed even though pain is of radicular distribution, as stated above, positive clinical evidence of such pressure may be elicited in the history and confirmed in the examination. In the history, sensations of paresthesia in the area of pain distribution, weakness of knee or ankle function, and increase of sciatic pain on coughing, sneezing or straining, constitute support for the diagnosis. The examination of the patient may yield certain evidence of root pressure. Consistent areas of hypesthesia may be detected, unilateral atrophy of the thigh or calf, and alterations in knee or ankle jerk and motor weakness indicate nerve root pressure more accurately than does the distribution of pain. For such examinations it may be useful to remember that the nerve root emerges one segment below its separation from the cauda equina. The disc of L3 may therefore be expected to produce pressure upon the L4 root causing pain which crosses the thigh anteriorly to the inner aspect of the knee joint. It may diminish the knee jerk and produce some quadriceps atrophy. The herniated disc at L4 can produce pressure upon the root of L5. Pain would be anticipated in the anterolateral aspect of the leg and the dorsum of the foot and weakness might present in elevation of the foot and the great toe. The ability of the patient to bear weight on the heel of the involved foot may be helpful in detecting such weakness. Retropulsion of the disc at L5 pressing upon the root of S1 can cause pain in the outer calf, in the side and under surface of the foot. The ankle jerk might be compromised or absent and plantar flexion may be weak. Inability to bear weight on the toes of the involved leg may reflect this weakness. As stated above, many factors can vary the accuracy of this picture, especially the frequent occurrence of pressure upon roots that emerge below. When the precise level involved is important—as for a surgical approach—myelography provides more accurate information.

5. *The radiograph.* Contrary to what might be anticipated, the sudden precipitation of disc retropulsion after no or short antecedent backache is not promptly reflected on the radiograph by disc narrowing. Presumably because

of the small range of motion at low lumbar spaces, disc narrowing and secondary hypertrophic changes may not be apparent until many months or even years after the acute attack has passed. As stated above, the function of simple radiography of the low back and pelvis is mainly that of excluding possible congenital anomalies such as spondylolisthesis (Fig. 8), spondylolysis or other skeletal variations or lesions of the low back and pelvis. The



FIG. 8. Severe spondylolisthesis producing minimal symptoms only after heavy lifting.

narrowing which is so common at the lumbosacral interspace is often developmental and does not necessarily reflect discogenic disease. When it is associated with osteoarthritic lipping, it indicates an old lesion of long duration. At higher levels the narrowed interspace is indicative of longstanding disruption. The disc that on radiography is markedly narrowed and osteoarthritic can be manifest clinically in smoldering symptoms resulting from secondary changes in bones and facets. It is not compatible with the cause of new intense sciatica which can be safely attributed to an adjoining newly involved level not apparent on the roentgen film (Fig. 2A, 2B).

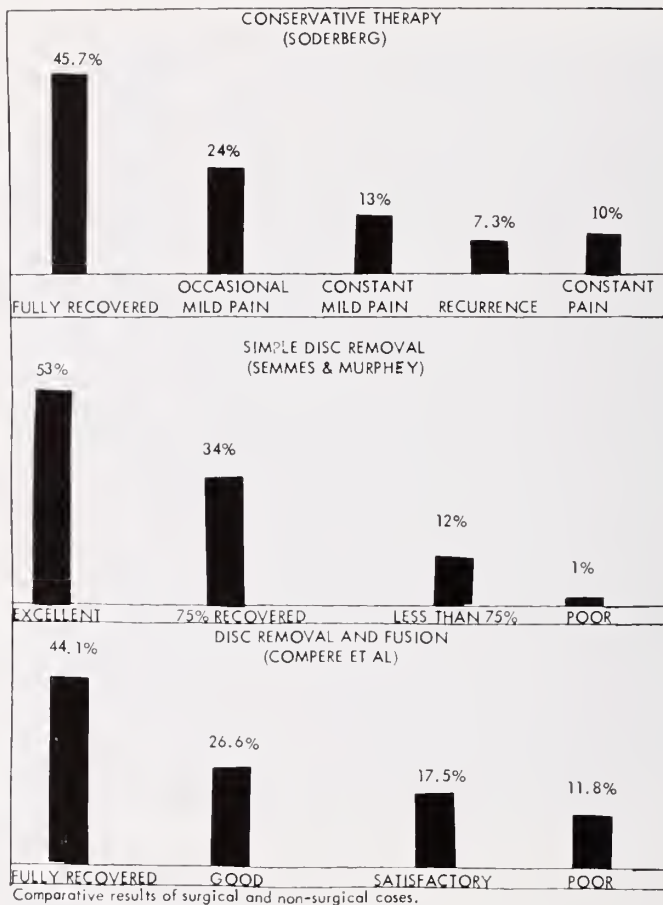
THE PLANNING OF TREATMENT

The planning of treatment for the individual patient must take into consideration many aspects, general and individual. When severe and crippling discogenic sciatica with evidence of nerve root pressure exists, the question of prompt surgical intervention as opposed to a trial of conservative therapy remains an area of controversy. Some highly skilled surgeons believe that any evidence of pressure on nerve roots calls for prompt removal of extruded tissue, perhaps supplemented by fusion of the adjacent vertebrae. Others, including the author, are inclined, with certain exceptions, to reserve the surgical approach until at least a fair trial of conservative therapy has failed to yield improvement. Exceptions would, of course, include the persistence or increase of intolerable sciatic pain on recumbency, a long history of unremitting incapacitating pain or frequent recurrences, the inability of some patients to accept prolonged recumbency, and especially, the findings of significant or progressive motor weakness or sensory loss. Recovery of motor changes may not occur unless root pressure is promptly relieved. Although the mechanism of spontaneous recovery is not clearly understood, clinical experience indicates that in suitable cases benign and lasting recovery may ultimately be anticipated in at least the proportion of cases indicated in Soderberg's study as reviewed above. In less violent cases, the response is even higher. In justification for the trial of nonsurgical therapy even in cases which show some evidence of nerve root pressure, Soderberg's eight-year results of conservative therapy are charted in comparison with the results of simple disc removal (17) and with the results of disc removal plus spinal fusion (18) (Chart 1). While these data emanate from different sources and were subject to the interpretation of different observers, they are sufficiently comparable to indicate that, in accordance with the concept of earlier times, sciatica is frequently self-limited and that after either the surgical or nonsurgical approach, recurrences are not too frequent. Although response to conservative therapy is slower and less predictable than that following excision of the herniated disc, few patients informed of the general picture would not elect a trial of relief without surgical intervention. Obviously the failure to improve or to evidence retrogression while the patient is on total bed rest would suggest resort to surgical operation. Those (including the author) who favor trial of nonoperative therapy, when unsuccessful, are eventually blamed by the patient for the "needless" delay of operation. However, such accusations are easily outweighed by the appreciation of those patients who have recovered and stayed well without operation.

The cardinal principle of conservative treatment is recumbency. Entirely empirical, its virtue is based upon long experience. The initial period of bed rest is continued for a period of at least two to four weeks and maintained for longer if there is some but insufficient progress. Since the purpose is to relieve the spine of weight bearing, the patient is not permitted to sit, but he may

roll from side to side and is encouraged to do so. Sometimes the application of pelvic traction is useful—more for the sake of assuring recumbency than for any direct benefit that might accrue from the pull of the weights. One or two pillows are usually allowed and occasional support under flexed knees may be useful in diminishing the pain. If the patient becomes dissatisfied

CHART 1

CHART 1. *Comparative Results in Surgical and Nonsurgical Cases.*

because of the apparent lack of more direct active treatment, very cautious mild physiotherapy may be employed, mainly for diversion. When the program of prolonged bed rest is utilized, regular periodic testing is important. The sensory, motor, reflex and Lasegue tests can be performed in recumbency and are important not only to determine progress but to detect the rare instances of retrogression that can occur even during recumbency. If and when sufficient evidence of improvement presents, the patient is provided with a back support (corset or brace) and permitted gradually increasing periods out of bed.

As pain diminishes, carefully guided exercises may be used to restore muscle tone and control while the discs of the low back are protected from undue strain. For those who have milder degrees of low back pain and sciatica, it is often possible to omit the the initial bed rest and to start the program instead with the back support. Much gain can result from careful analysis of the patient's daily activities. It is surprising how often violent calisthenics, long-standing, jolting commuting trips, and even tennis games or horseback riding may constitute so important a part of the life of the patient that they are pursued with no awareness of the relation they may bear to the persistence if not the cause of the low back-sciatic syndrome. Similarly, the constant stooping required for daily multiple bed making and heavy lifting must be discovered and eliminated if recovery is to be expedited. Instruction in the performance of essential chores such as bending at the knees rather than the low back is of help. Also of considerable value is the recommendation that daily recumbency be increased to twelve or even sixteen hours. In mild cases, the simple control of daily activities in this way may suffice to dispel the symptoms.

As might be expected, these measures usually give relief for the current episode only. When the history discloses a long series of previous attacks, the choice rests between permanent curtailment of activities which cause back strain or rehabilitation by surgical operation. Although recurrences of severe sciatica are relatively rare, they do occur, as do longstanding cases unresponsive to conservative treatment. In such circumstances, and in cases which exhibit major neurological findings, surgical operation offers the only prospect of lasting relief. Extruded disc tissue requires excision and, in the author's opinion, fusion across the involved spinal level adds permanence to a favorable result.

The question of whether or not fusion should be added routinely to simple removal of the disc still remains controversial and beyond the scope of this paper. Young and Love (18), Barr (19), Stinchfield (20), and Compere (21) favor fusion, while Bucy (1) and Semmes and Murphey (17) have expressed the contrary view. Their reasons are available in the writings mentioned.

SUMMARY AND CONCLUSIONS

On the basis of our knowledge—and lack of it—about discogenic sciatica, the present study stresses the importance of painstaking and comprehensive observation of the individual patient who suffers from pain radiating into the lower extremity.

The nerve pathways that may reproduce sciatic pain are reviewed, together with examples of the many lesions that may be responsible. The most frequent offender, the disc lesion, is then described from the viewpoint of pathology. Its development and anatomy are touched upon, together with the more recent concepts concerning the distinction between the physiological evidences of aging and those referable to pathological disruption.

From the clinical aspect, the curious discrepancy between irreversible dis-

ruption and its sciatic reflection, which may be transitory and often self limited, is emphasized. The not uncommon occurrence of entirely painless but severe disruption of discs is also mentioned, together with statistical support of the relative infrequency of recurrences of acute sciatica and its frequent and lasting arrest following nonsurgical therapy. Accordingly, discogenic sciatica may be often properly considered apart from its known pathological basis and does not necessarily require removal of extruded disc tissue or fusion of the adjacent vertebrae for the relief of symptoms.

The importance of careful and detailed clinical study of the patient cannot be overemphasized for the elimination of nondiscogenic lesions, for the elimination of contributory causes which may play a role in causing pain, and for the planning of treatment. The various aspects of this study are considered separately and their relation to surgical and nonsurgical therapy is indicated. The applicability of various therapeutic measures is discussed in the light of the survey of the patient.

Paramount is the principle that, although disc disruption is the common offender, the problem of therapy remains clinical and individual and dependent upon the careful and sustained observation of the patient. Therapy cannot be cursorily pigeonholed.

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Observation in Ophthalmology

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"Observation is the indisputable foundation for medical thought..."

Sigerist

Observation, as the term is used in medicine, is the act of watching attentively and gathering data from scientific studies in which facts or occurrences are recognized and noted (1).

The Latin source of the word "observed" is *ob-servare* meaning to save or to keep. From this root meaning two terms have come into English, namely *observation*, a later term with which we are concerned here, and *observance*, an earlier term which means to heed, or celebrate or keep rules, customs or rites. While I shall not be considering this second meaning extensively one cannot disregard it entirely for it can readily be seen that when one gathers data or watches attentively the *selection* or *saving* of certain parts and rejection of others is inevitable, so that the relationship of the whole basic idea of the term becomes apparent in its medical usage.

If we turn to the Latin from which the word springs, further understanding of connotations can be obtained (2). *Observatio*, f., (*observo*) was used by Cicero: *summa erat observatio in bello movendo*. The term suggests care, accuracy, exactness and circumspection; all of these ideas are present in our current medical use of the term observation. The Romans also spoke of observing nature and used the term *animadversio* (*notatio naturae et animadversio*), giving "observation" the meaning of attending to. They spoke of observing the stars (*observatio siderum*) and gave to the power of observation the characteristics of acuteness (*ingenii acumen*). It is interesting that the first observations of acuteness of vision were based on the ability to distinguish single from double stars. It was the astronomer Hooke who in 1705 determined the minimum separable as one minute of arc, a theory on which the elements of subsequent tests of vision were based. Later observation further reduced this figure. The Latin terms an observer, *speculator* (*speculator venatorque naturae*), an observer of nature, that is, one who looks out, thus bringing vision firmly into observation.

With these meanings of observation in mind, it could hardly be questioned that ophthalmology is especially justified in concerning itself with observation. Ophthalmology is the medical study of vision, of the structures and functions that subserve vision in health, and of the pathological variants of these with their causes and effects and treatments in disease. Observation being partly a visual act, it belongs in the realm of interest of ophthalmology.

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The second reason for ophthalmology to take interest in observation lies in the fact that observation, as Sigerist said, is the foundation for medical thought, and ophthalmological thought remains medical thought from a special viewpoint.

We may not assume that scientific or medical or ophthalmological observation is something totally different from the observation used by us all as a significant part of ordinary life at every turn. It is not, of course, although the scientific use of this natural endowment of man to perceive meaningfulness in himself and in his surroundings is merely that same faculty that we use casually in everyday life but which in the sciences is brought near to its ultimates of expansion (as in astronomy) and constriction (as in microscopy) and which is both generalized to serve an explanation of the stupendous flashes of cosmic forces and particularized to serve concentration on the tracing of single atomic particles.

In ophthalmology these widely divergent scientific aspects of observation have full application in a wide range of physical, chemical, and biological relations. But as in medicine generally, observation is at work also on the clinical side where one's powers as an observer are constantly being tested across a broad spectrum of diagnostic and therapeutic responsibilities which range from discovering the alterations of ocular tissues to the measurement of optical requirements and to the disturbances of behavior which result from ocular or visual loss or disturbance.

The discerning clinical and research ophthalmologist inevitably and repeatedly is brought face to face with the necessity to refine and use his most discerning powers of observation. These powers are based on the sense of vision although other senses, especially touch, may play a role. I have often considered that, in view of the neglected state of the senses of our young medical graduates, some practice designed to enhance perceptual powers would be in order. Observation presupposes the ability to direct and to concentrate one's attention volitionally on the desired elements of the total visual world, and it presupposes trained retentiveness (saving) of selected data observed. Thus, I have wondered if some practice in visual tasks might not be devised that would be useful in training medical students to observe more critically. It seems obvious that we cannot tolerate any further perpetration of the myth of infallibility of instrumentation in medicine if we are to regain the refined use of our senses. The very existence of a symposium such as this implies a need to re-emphasize observation, and observation is based on personal attributes that can be trained and brought to flower. In ophthalmology, for example, one may ask whether the tonometer should replace the fingers gently palpating the firmness of the eyeball? Should x-ray air studies of the orbit replace the palpating fingers on the tumor mass? The same questions apply to many medical problems outside ophthalmology, as well. Should the student learn to observe the patient's effects on instruments while neglecting effects in the patient himself? If we continue to yield to the mechanical side of medicine in an uncritical way, observation in medicine is bound to suffer, as it has already. What do we

stand to gain and what might we lose by continuing this recent abdication or neglect of observation of the patient in medicine?

The proponents of this abdication point to the fact that instrumental observation is more precise and dependable than observation by the unaided senses. The question, of course, is whether this accurate observation is really observation of the patient or whether it is, at times, observation of the machine and its effects.

The opponents of this trend lament the dehumanizing and depersonalizing influence on medicine of such an emphasis on the partial effect which is embodied in the machine. They demand the ultimate introduction of the partial observation into a larger observation of the *whole* of man, or disease, or health, or vision. This is requisite if the true complete significance of the part is to be attained.

Indeed, they say that the selection of the part that is to be observed depends initially on the fullness of observation of the dynamic whole and on the scope of understanding that results from full observation in the first place.

The latter view seems to me to take the most of the problem into account and, for this reason, it seems to point to a more fruitful ultimate realization of both generalizing as well as particularizing observation in medicine. These two terms are selected with care. They exemplify the fact that observation, as I am considering it, goes far beyond sensualistic aspects to include intellectualization, comprehension, evaluation and the establishing of relationships. There is then, as I understand the term, a synthetic and holistic nature in observation. One might say there is as much sense as there is sensation in observation. Indeed, truly meaningful vision is reached only when this highly personal, synthetic element is achieved. Such vision, which is prerequisite to observation, includes the whole organismic concept that we call man.

In ophthalmology, these two aspects of observation have interacted from the very beginning, although it is chiefly generalization that is associated with primitive and archaic medicine while the attention to observing particulars grew little by little until it finally dominated medical science in the nineteenth century and even in much of our own century. It is only a recent departure of medical thought to observe once again total, integrated man and disease, and there is promise of a continued strengthening and ordering of medical concepts by this means in the future without forfeiting any of the technological advantages.

As I have noted in previous writings, ophthalmological history closely parallels general medical history. This is apparently due to the general action of cultural, philosophical and scientific trends and developments of an age on the whole of medicine including ophthalmology. Observation being largely a visual act, we should expect both what is selected to be observed and what is observed therein to be quite different at different times of history; this is very much the case. I believe that we can attain a fuller sophistication of observational potentialities in ourselves if we observe how past contributors to ophthalmology looked at the same things that we see, and how they interpreted and gave their

own values to what they saw, and how these interpretations and values match or are different from our own.

HISTORICAL CONSIDERATIONS

We may begin with observation itself. Vision, which as I have indicated is the keystone of observational powers, and the eyes as the organ of vision, were and still are considered to be of the highest value by primitive people. Observational powers, using vision principally, constitute the best insurance against natural enemies and destructive forces. A blind man in the chaotic surroundings of primitive existence is bound to fall or to be felled. By extension, this power of observation to protect and preserve, to find meanings, to guide actions and to bring health and life to man, was considered to be, in its most highly developed form, a god-like attribute. Thus the omniscience of the gods was based on the all-seeing eye. Indeed the human possessor of great vision, that is, one capable of collecting extensive data, and of ordering and maintaining understanding gained by personal observation of life and its ways, came to be revered, praised, hailed and finally deified. This was true of such early figures as Imhotep, Horus, Aesculapius, and others. A touch of this reverence can be felt especially among the laity regarding such recent medical figures as Sir William Osler, Sir Alexander Fleming, Madame Curie, Louis Pasteur, Harvey Cushing, Albert Schweitzer and others.

Today we live in a more orderly world. Cities are divided into regular blocks. Streets are wide and straight. Sidewalks are high and free of obstacles. Traffic is regulated by signs and lights. Houses are arranged logically by plan and work places have dependable arrangements as well. Here, while there are certain challenges and even threats for the blind man, to be sure, and while blindness means tragedy and isolation in many ways, it no longer need signify death. Survival of the blind has been enhanced by social forces which aim to educate, enlighten, cheer and sustain the blind persons among us. In return the blind have rewarded society with many contributions to labor, the arts, the profession and politics. The disapprobation of blindness has been greatly modified by modern civilization; interestingly enough, the mystery of vision has been largely devalued as well. In truth vision still remains as much a mystery as life and thought and memory, and all these are components of observation. Thus, in its essence we cannot discuss the "what" of observation but only how we use it. Nevertheless, among intelligent persons today there no longer remains any superstition attached either to vision or to the loss of it. The evil eye is looked upon today as an amusing relic as is the oracular power attributed to blind soothsayers. But in mythology eyes figured strongly, from the single eye of Cyclops to the hundred eyes of the Argus; the extent of observational powers and therefore the formidableness of an adversary rested upon the numbers of these organs of observation. Thus from the earliest times man recognized the relation of vision to power and used the destruction of vision as the definitive means for limiting or destroying power. Power, whether personal, scientific, or military, is based largely upon observation; it is for this reason that outside of science, perhaps the most important use of observation is in the

military. Thus the generals of every age have depended upon their observation posts. Is not medicine a sort of war with the forces of preservation opposing the forces of destruction? The physician assembles his armamentarium, observes the characteristics and virulence of his enemy and then directs his therapeutic attack, but the patient is more than the battleground of this conflict. In recounting the facts of his pathography he is a partner with the physician, sharing the effort to observe correctly his own diseased state within the scope of his ability and guided by the physician who, by experience and knowledge, knows where to look and what to observe. The physician knows that the patient, while in effect he *is* the disease, is also much more, namely the potential ultimate victim of his state of disease. Thus the physician observes not only diseases but the pathos of man. At this point, observation assumes a new and more noble and personal character. It is here (as indeed it was with Hippocrates 2400 years ago) that observation demands an important new vestiment, namely that of ethics. What we observe then determines many collateral things, not the least of which is a moral setting in which the observation can be conducted. The privilege to observe presupposes protection of the observed. As a consequence partly of this side of observation, a special set of laws and mores related to the physician has evolved, beginning with Hammurabi's code and involving religious doctrine and common law ever since to our own day.

It was the ancient Greeks who introduced this shaping of observation of man in disease and it was the Greeks (specifically Hippocrates) who formulated (or adopted, as Ludwig Edelstein holds) a suitable code of ethics to accompany it. The Greeks noted and recorded for us their observations concerning many external ocular disorders such as trachoma, which they treated by abrasion (ophthalmoxysis), cauterization and even peroxide of copper. They also recorded their observations of pterygium, chalazion, and entropion. Their observations extended beyond the external disease, however, to posthaemorrhagic amaurosis, nystagmus and strabismus. Much remains to be learned about their concepts of cataract and glaucoma, but it is generally assumed that they confused these two diseases. Thus, their observations led them to know the course of eye diseases; by means of this, highly accurate prognoses could be made and on this basis limited treatments could be instituted. Diagnosis and classification were of little importance in Hippocratic medicine as developed on the Island of Cos although they were more important to the Cnidian School.

Plato hypothesized that vision was the product of an outflow of "fire" from the eye that mixed with an ethereal, external fire. This idea was compatible with his man-centered philosophy. It is possible that his idea sprang from his observation of reflective animal eyes. Aristotle (384-322 B.C.), who was Plato's pupil, differed with his great teacher on this important point, observing that man cannot see in the dark. He derived the first sensualistic concept of vision as being the result of an inflowing influence on a receptive organ, although he had no knowledge of the physics of light. He also made observations of the weak sight of old age and of the anatomy of the eye.

Aristotle was not content to leave vision itself on a purely sensualistic basis.

He said, "What perceives is of course a spatial magnitude, but we must not admit that either the having the power to perceive or the sense itself is a magnitude; what they are is a certain ratio or power in a magnitude" (3).

While acknowledging Aristotle as the source of a sensualistic concept of perception, we are concerned equally to acknowledge his even more profound metaphysical expression of the power to perceive, *i.e.*, of the visual sense itself, the eye being only an eye in so far as it is an "actualized" visually functioning, integral part of the total human organism.

Observation in ophthalmology, as well as medicine in general, became strongly anatomical in the hands of the greatest physician and anatomist of antiquity, Galen (A.D. 129–200). The search for a physical anatomical seat of vision was diligently made. For Galen the essential organ of vision was the crystalline lens, the retina being an extension of the brain which conveyed the changes in the lens to the brain. Although Galen retained vestiges of both Platonic and Aristotelian concepts of vision, he did not fail to observe that there are two eyes and that vision with two eyes is different from vision with one eye. Thus he initiated interest in binocular vision and called attention to what can only have been an auto-observation, namely, that one can see around more of a column with two eyes than with only one. He related this functional observation to his anatomical observation of the two optic nerves and the chiasm.

Galen's observations of the anatomy of the Barbary ape led him far along the road to understanding the anatomical structure of man, but he was wrong in several crucial areas, specifically, the heart, the brain and the eye. If his investigational tradition had continued uninterruptedly, instead of being replaced by a tradition of disinterest in this world, corrections of these errors undoubtedly would have come much earlier. The fact that this did not happen is perhaps the most significant proof of the interaction of general cultural influences on science and medicine.

It is interesting and a bit disquieting to realize how completely and rapidly men ceased, for the extended period known as the Dark and Middle Ages, to exert their powers of observation. Symbolically they closed their eyes in prayer, severing visualization of their natural existence, and fell into their litanies of faith which came to include finally even Galen's teleological anatomical concepts. Dressed in the armor of church sanction, these tentative beginnings chained, confined, and finally rusted away the investigative minds of all but a few, brave exceptions.

Among the great exceptions was the Franciscan friar, Roger Bacon (1214–1292), the medieval scholar who opened the way to earlier writings, especially those of Aristotle, through his grammar of the Greek language. Bacon was the great and original Western contributor to optics who led to the therapeutic use of glass lenses. This great ophthalmological innovation sprang from the herald of the experimental method.

The experimental method, the classical basis of scientific thought, rests squarely on observation.

In the Eastern or Arabic medieval world, characterized by strong mathe-

matical interests and originality, Ibn-Al-Haitham (Alhazen) (A.D. 965–1039) began to solve problems of reflection from mirrors and refraction by lenses. Once again, a momentous contribution was derived from homely observation. A stick half submerged in water must have appeared angulated to many observers before Alhazen, but it was he who finally observed the consistencies of this phenomenon and others as well, such as the inverted image produced by light passing through a chink in a wall into a dark room, which later came to be known as the camera obscura (della Porta, 1540–1615).

A new avenue of investigation was opened by Alhazen's treatises on optics and light. Anatomy was given a new purpose, namely to find a structural basis for optical imagery. More than this was the anticipation of the union of physics and sensation that was to grow in seventeenth century baroque iatrophysics and to flower in the physiological optics of the Romantic nineteenth century.

A Jesuit priest, Christoph Scheiner (1575–1650), directly observed and then demonstrated the inverted retinal images through posterior windows cut in the sclerae of enucleated eyes. This disconcerting fact had been avoided or missed by Leonardo de Vinci, who, despite his many other correct and valuable anatomical observations, had re-established an upright image in his optics of the eye and made the further error of projecting it onto the optic nerve head, which is actually the only insensitive part of the retina. This may have sprung from faulty models of the eye which he constructed or possibly from artistic reasoning that might have denied the logic of an inverted image in the eye. Even today many persons erroneously believe that the "image" is turned upright in the brain, but anatomical and neuropathological studies have established that the cerebral representation in the brain of the retinal areas remains inverted and reversed. This may tend to disturb mechanistically minded persons who, although they would probably deny it, seem still to be looking for precise isomorphic representations of outer objects in the brain much as the pre-Socratic Greek philosophers who explained vision as resulting from the entrance into the eye of small images or *eidola* from objects in the outer world. This misconception probably can be related to observation of the reflected, minified images that can be seen in the pupil. Thus, uneritical observation, like a little bit of knowledge, can be dangerously misleading.

At the close of the eighteenth century, a figure of versatility, imagination and originality appeared. Thomas Young (1773–1829) was a man of especially keen observation coupled with wide and deep intellect. Within his realm of interest fell such widely diverse studies as the translation of the Rosetta Stone, as well as medicine, physics, physiology and what is important here, physiological optics.

Young, observing his own prominent eyes, took the opportunity to measure them physically and to prove his theories of astigmatism and accommodation. In this he became both his own object of observation as well as the observer. Every grade of such auto-observation can be found in medicine and science. At times this is dangerous but often it is dramatic and fruitful.

The next great contributor to physiological optics was Cornelis Donders

(1818–1889), who observed that crossed eyes occurred most frequently in far-sighted patients and that wall eyes accompany myopia chiefly. From this observation came his concepts of the relation of refraction to strabismus or what we call accommodative squint.

Perhaps the high point of the relating of physics to sensory physiology came in the later nineteenth century when Hermann von Helmholtz produced his *Handbuch der Physiologischen Optik* (1856) based on observations facilitated by instruments which he invented especially in order to extend his vision into the inner recesses of the eyes. This was his *Augenspiegel* (1851), which has come into our hands as the ophthalmoscope. This instrument did much more than open new doors to ophthalmological practice. It heralded an entirely new era of endoscopic examination. With the advent of the otoscope, laryngoscope (produced by Manuel Garcia, a voice teacher in London in 1854), bronchoscope, gastroscope, etc., it became possible not only to observe new areas of the living human body, but to direct new and controlled diagnostic and therapeutic measures toward these previously forbidden areas.

Physical enhancement of observational methods in ophthalmology grew rapidly from that point on. The electric ophthalmoscope of May was a refinement of the *Augenspiegel*. Gullstrand's slit-lamp biomicroscope, which won him the Nobel Prize in 1911, permitted another entirely new view of the ocular tissues by making an optical section through the optical media and the retina. Soon new tomes describing observations based on this technique became available and popularized the technique. The ophthalmoscope became the ophthalmologist's right hand, his slit-lamp became his left hand, in observing ocular diseases and their effects.

Physics in ophthalmology has led us to deeper and deeper investigations of the eye through electroretinography, tonography and sonograms. The possibilities of these extensions seem almost endless. But, as I have noted above, observation here, while it is highly useful, only concerns the patient indirectly.

Having sketched briefly the influence of observation on the development of physiological optics and mechanistic or physical concepts of vision, I should like to refer to the manner in which observation has entered clinical considerations.

CLINICAL CONSIDERATIONS

In the eighteenth century attention came to be focused on the true nature of cataract. As I have mentioned, a confusion between cataract and glaucoma had existed for centuries. During the Age of Enlightenment, means to "enlighten" the eye were being eagerly sought, and it was largely in France that both general and ophthalmological enlightenment were occurring. Thus we find the great *Traité*s of Maitre-Jan, St. Yves and Daviel on cataract. Dechaes observed that patients whose cataracts had been removed required strong convex lenses in order to see clearly. Previously it had been believed that the cataract was a dried humor in front of the lens in a presumed (but actually nonexistent) space between the crystalline lens and the iris. It was

thought to be this membrane that was depressed from in front of the lens. Since the lens was thought to be the seat of vision, the idea was never entertained that it was the lens itself that was displaced in couching a cataract. To accept this would have amounted to contradicting the traditional theory of the site of vision, and this was impossible in the earlier periods. However, by 1656 Werner Rolfinck indicated that cataract is the lens which had become opaque. This opinion was based on anatomical studies. These facts were rediscovered in 1705 by Michael Brisseau (1696–1743), a surgeon whose views were supported by Maître-Jan in 1707. In the same year Charles St. Yves (1667–1736) removed a broken crystalline lens from the anterior chamber of a patient's eye during paracentesis of the cornea, a much older procedure used to evacuate pus from the eye. The following year this feat was repeated by Jean Louis Petit. These observations bore definitive fruit in 1745 when Jacques Daviel (1696–1762) deliberately planned and carried out extraction of cataract, through a corneal incision, from the normal position behind the iris (4). Daviel operated on four hundred and thirty-four cataracts by 1756 and claimed 88 per cent success. While there have been refinements ever since, extraction remains the only important treatment of cataract to this day.

The other condition, glaucoma, had a great turning point exactly one hundred years ago when Sir William Bowman (1816–1892) observed that there is an "augmentation" or "exaltation" of the intraocular tension above the range of normal early in glaucoma. Glaucoma had gained its name in ancient times from the greenish, dilated pupil seen in a fullblown case in which the eyeball has become hard. By the time these findings are present, the insidiously destructive pressure that characterizes the disease has already done irreparable damage to the sensitive and susceptible retina. Some way to institute early treatment had to be found. Bowman found that by simply palpating eyes gently with his two index fingers he could distinguish nine grades of intraocular pressure. Using this new application of his observational powers, Bowman operated early in the disease and prevented blindness. The diagnostic technique soon led to the invention of the tonometer. Our own age has produced an electronic version of this instrument for tonography.

Bowman's contemporary, Albrecht von Graefe (1828–1870), contributed the surgical procedure of iridectomy for glaucoma, a procedure still in use today with modifications. He also noted the pulsations of vessels on the optic disk in glaucoma, and he observed that the upper lids lag when patients with exophthalmic goiter look down (Graefe's sign). He also made countless other contributions based on his avid curiosity to understand ocular disease. Von Graefe shaped the practice of ophthalmology as a distinct discipline much as we know it today.

Von Graefe, observing the fundi with Helmholtz's *Augenspiegel*, contributed many descriptions both of intrinsic diseases of the retina and choroid and of general systemic diseases which are revealed by effects in the eyes. By virtue of being the first ophthalmologist to use the ophthalmoscope, von Graefe had the great privilege to be the first to observe the changes in the retina and optic

nerve that accompany visual loss without interference to the passage of light into the eye and the formation of a sharp image on the retina. The solution to the age-old problem of *gutta serena* or amblyopia without opacity (*gutta opaca*) lay in his hands. In 1859 he observed the fundus of a patient who suffered from sudden loss of vision. He noted the effects of embolism of the retinal artery, which results in a pale edematous fundus with empty vessels or segmented blood along the retinal arterioles and the red spot at the macula where the deep, red circulation of the choroid was plainly visible. This observation led to rapid therapeutic efforts that are sometimes successful, if instituted immediately, in preventing total loss of vision.

Another difficult problem had been the distinguishing of functional or hysterical blindness from organic loss of vision. Once again the extended powers of observation supplied by the ophthalmoscope enabled von Graefe to diagnose optic neuritis by observable changes in the color and form of the optic nerve and thus to distinguish it from hysterical blindness in which the intraocular tissues are not involved.

Many new therapeutic advances were based on the new ability to see into the eye. Now it was possible to see detached retinas with holes and tears. From this observation came efforts to replace the retina to its nourishing choroidal bed and to close the rents and disinsertions. Jules Gonin (1870-1935) in Switzerland introduced thermocautery in 1914; this was rapidly improved upon by C. B. Walker and H. S. A. Gradle. The most recent improvement was light coagulation, an entirely new nonsurgical approach introduced by Gerd Meyer-Schwickerath in 1958. The blindness produced by observing direct sunlight, especially during eclipses of the sun, had been observed since ancient times. Even the effects of retinal burns were long known to ophthalmic pathologists from Czerny in 1867 to Maggiore in 1927. Meyer-Schwickerath has written, "My interest was aroused by *personal observation* of a number of patients with macular damage following the eclipse of the sun on July 10, 1945. . . a few days after I saw this patient (in 1946) I became aware of the clinical application of light coagulation. It took four years of work to translate this idea into the first clinically usable instrument. Many unsuccessful experiments, during the first few years cast doubts in my mind as to the feasibility of light coagulating the human retina, but I was always encouraged to go on by the *clinical observations* of retinal damage as the result of light energy" (5) (italics mine).

In reading this statement we cannot fail to be impressed by the fact that both the initiating factor and the sustaining reassurance in the face of doubt was observation.

Meyer-Schwickerath's work moved from use of a crude device designed to direct sunlight into the eye to use of a carbon arc (Beck, 1951) and finally to a Xenon high pressure lamp. Its application has broadened to include von Hippel's retinal angiomas, Coats' exudative retinitis, Eales' disease, retinoblastoma and small malignant melanomas.

Undoubtedly this departure to an entirely unique therapeutic modality,

which I heard introduced (and ridiculed by a famous continental ophthalmologist) at the International Congress of Ophthalmology in New York in 1958, will be one of the summits of twentieth century clinical ophthalmology.

One of the most interesting advances in understanding of the basic nature of vision was made by Adelbert Ames, a lawyer working at Dartmouth Laboratories, who made auto-observations of the way one sees with one and two eyes. These studies led to experiments in the psychology of vision and discovery of the concept of aniseikonia. This condition, in which differences in the size of the two retinal images produce disturbed space perception, can also be responsible for asthenopic symptoms. Aniseikonia is important since it bears on what one observes and illustrates the important relationship of our observations to proper vision.

In the field of recent (1958) ocular surgery, observation by Joaquin Barraquer of the selective effects of an enzyme, alpha-chymotrypsin, an endopeptidase, on the zonular fibers of the lens, has led to improvement of the facility of cataract extraction.

CONCLUSION

The examples that I have selected illustrate the importance of the historical relation between observation and the development of the ophthalmological mind. Doubtless other significant examples could have been chosen, but there can be no question that observation always has made important contributions to ophthalmology and always will.

Finally, I wish to note that for me the ophthalmologist remains a physician first, a surgeon second, and a specialist last. As a physician, he meets his patient as a complete and integrated totality and this figure or person of the patient remains foremost in the ophthalmologist's consideration of him. Thus, as the patient first approaches, the ophthalmologist has the opportunity to observe his manner, gait, speech, and movements, all of which contribute to an understanding of his visual function in life. To neglect these clues of the practical efficiency of his vision or to fail to learn the patient's age, personality, environmental settings and occupational requirements while leaning heavily on the patient's test performance in the office would be to leave oneself open to miscalculation of his needs and potentialities. Sloane has thoughtfully pointed out (6) that the mere figures in a vision test do not necessarily establish a basis for operability. Such isolated observations must be cast in the framework of individualizing the patient's ability to respond to and profit from surgery and the new sort of vision that ensues even when the results postoperatively so far as a single test, namely the visual acuity test, appear very favorable when compared to preoperative test values. It would be just as shortsighted to throw all patients of a given chronological age into one category. Everyone sees that individualization of age is necessary. What is harder to perceive is that all such generalizations ultimately demand individualization, and that this is based on careful observation not of a test or an ocular tissue, but of a person with a history and a future.

Here is the place where a specialist remains a physician even within the confines of special practice. In addition, the specialist so oriented to view the whole, cannot help but note health problems germane to other specialties and to refer the patient for attention to these. Ophthalmology is especially suitable to the discovery of systemic diseases. Observant ophthalmologists thus serve the general physician of the patient in confirming or discovering many ailments that affect the eyes. The fundus, for example, is the only place in which we can conveniently see living nervous and vascular tissues, a fact that brought the ophthalmoscope almost immediately upon its discovery into the hands of neurologists (Hughlings Jackson) and internists (Sir Clifford Albutt). Indeed it was they who popularized its use generally in medicine to the point that today no medical examination is complete without observation of the fundi.

Thus observation permeates every phase of ophthalmology, and its refinement in the service of this specialty has served to illustrate and enhance its usefulness to medicine as a whole.

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Observation in Dermatology

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Simple observation is of prime importance in dermatology. In most instances the careful and methodical observation of patients with cutaneous disease will give sufficient information for diagnosis. The physician should be trained to observe the normal and pathologic skin methodically. In gathering the necessary information he will usually be able to arrive, step by step, at the correct diagnosis. Many systemic conditions may cause alterations of the skin, nails, hair and mucous membranes; these changes are helpful in diagnosis. They may pass undetected if careful, methodical observation is not employed.

Observation of the patient affected by a disease of the skin may be divided into two parts:

- 1) Observation of the patient as a whole—his skin, nails, hair, mucous membranes, and clothing.
- 2) Observation of the dermatosis, if such is present.

OBSERVATION OF THE PATIENT AS A WHOLE

Examination of the skin and its adnexa requires good diffused daylight and a room with a temperature pleasant enough for the disrobed patient. If artificial light is available a soft blue light or a "daylight" type of electric bulb is essential.

The objective signs of cutaneous diseases are chiefly those which are appreciable by sight. Palpation of the lesions, observation with the tips of the fingers, gives information as to the degree of infiltration and tenderness. The sense of smell assists in the diagnosis of some conditions, such as favus, pemphigus foliaceus, and *Pseudomonas aeruginosa* infections.

Observation of the patient conducted in order to understand him as an individual requires a step-by-step procedure which an experienced observer can perform quickly; the less experienced observer should follow a certain order to avoid overlooking information which may be valuable in the general inventory of the patient.

In the general inventory attention should be paid to: age, sex, race and national origin, occupation, personal hygiene, color and texture of the skin and condition of the nails, hair and mucous membranes.

The *age* of the patient may serve as a clue to diagnosis. As Stelwagon has stated, infancy, youth, maturity and old age all have their cutaneous vulnerabilities. Psoriasis, fungus infections of the feet, lupus erythematosus, pemphigus vulgaris and lymphoblastoma are rare in children, while impetigo,

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popular urticaria or prurigo mitis and warts are common. Acne is predominant in adolescence, while rosacea and seborrheic dermatitis are seen in the adult. Venereal diseases are more common in young adults, although recently an increase has been noted in teen-agers. Ringworm of the scalp is common in children and exceedingly rare in adults, in whom it is caused by *Trichophyton* which does not fluoresce under the Wood's light. In the elderly, keratoses, seborrheic and senile, cutaneous carcinoma, pemphigus and pemphigoid eruptions, lymphoblastoma, dermatitis hiemalis and varicose eczema are common.

The sex of the patient may also be helpful in diagnosis, as some diseases are more common in one sex than in the other. Collagen diseases, especially lupus erythematosus, are more frequent in women. Kaposi's sarcoma is rare in women. Lichen sclerosus et atrophicus is more often seen in women. Paget's disease of the nipple is seen exclusively in women; the extramammary type affects men also. Carcinoma of the lower lip is seen almost exclusively in men, especially in pipe smokers.

Certain cutaneous disorders are seen in *special physiological states*. Prurigo, herpes gestationis, filiform growths and pigmentation may develop during pregnancy; vulvar pruritus and plantar and palmar keratoderma may appear during menopause.

Race and national origin may offer diagnostic hints. It is well known that in the Negro the incidence of psoriasis, pediculosis and cutaneous cancer is low, whereas the incidence of keloid and of sarcoidosis is relatively high. Pemphigus appears to be more common in Mediterranean peoples. Intestinal parasites are common in patients from the Caribbean and should be suspected in cases of anal pruritus. Patients originating from areas where leprosy is endemic should be suspected of having this disease if erythema nodosum, peculiar eruptions, or neurologic symptoms are present. The Nordic people because of their whiter skin are especially susceptible to damage by actinic radiation and to cutaneous cancer. A leg ulcer in a young Negro should immediately suggest sickle-cell anemia.

Filth contributes to cutaneous disease among the poor and neglected; pyogenic conditions spread rapidly and oozing dermatoses become secondarily infected. Conversely, extreme cleanliness and the injudicious use of soap and water is sometimes responsible for the production or aggravation of certain dermatoses, such as chafing, miliaria, dermatitis hiemalis, and nummular eczema. This is especially true in the aged whose skin is somewhat atrophic and lacks the natural oils that lubricate the skin. Insufficient use of soap, not necessarily to the point of uncleanness (as is often seen in boys) aggravates acne and keratosis pilaris.

Overdressing and the use of flannels and wool directly on the skin may be a factor in the development of some dermatitides. The use of certain materials, such as the nylon and rubber in girdles, interferes with the normal function of the skin and may predispose to miliaria. Heavy shoes and thick woolen socks aggravate dermatophytosis of the feet.

In his *occupation* the patient may come in contact with substances that

cause cutaneous changes. A knowledge of the latter may enable the physician, by simple inspection, to recognize the patient's occupation. The substances handled and the instruments or tools used may affect the skin through pressure, friction, and mechanical or allergic action. The most common of these stigmata are the callosities which develop on the hands of mechanics, carpenters, shoemakers, musicians, and others. The exact location is characteristic of each trade and depends on the type of tool or instrument used and the locus of contact. Other cutaneous disorders such as contact dermatitis, paronychia, and moniliasis, are common in persons such as dish-washers and soda-fountain employees, who engage in "wet work" which requires constant immersion of the hands in water. Another type of stigma is found on the lower extremities, *e.g.*, hyperkeratosis of the knees of cleaning women. Fibrotic nodules of the skin on the shins of painters are traumatic and are caused by pressing against ladders with the legs. In miners the skin, especially over the upper part of the body, may show a blue-black tattoo caused by impregnation with coal dust.

Observation of the *color* of the skin may be of definite diagnostic assistance not only in skin disease, but also in many systemic disorders.

In any individual the color of the skin depends on a variety of factors, of which racial origin, general health, and degree of exposure to sunlight are among the most important. The normal color is affected to an important degree by its vascularity, by the thickness of the epidermis and by the presence of the normal pigments. Careful study of the variations of color among many individuals of different ages and races will enable the observer to gather enough experience to detect minimal changes that may be of diagnostic significance.

The abnormal variations in the color of the skin may be briefly divided into those that present a yellowish tint, the hyperpigmentation of a brownish color, and the hypopigmentation of a whitish color. Vascular changes may produce a reddish to violaceous hue. The pallor of anemia is especially evident in the palmar creases when the palm is stretched and compared with a normal palm. In pernicious anemia the skin is icteric and waxy. In iron-deficiency anemias it may be yellowish-green with a brownish hue.

Among the yellowish pigmentations of the skin jaundice is the most common. The color varies from faint yellow to orange, saffron, yellowish-green, green, and even bronze or dark brown. These different hues are believed by some to be of diagnostic significance.

An increase in the normal carotene pigment leads to a canary or lemon hue of the skin, especially in the palms, soles and face. The absence of yellow discoloration in the sclera immediately differentiates this condition from jaundice. It has been suggested that the yellowish hue of patients who have long-standing renal failure and myxedema are due to the presence of carotene. The ability of atabrine to cause a yellowish discoloration of the skin became well known during the Second World War. It can be distinguished from carotinemia by the deeper pigmentation of the dorsum of the hands in the former, and on the palms and soles on the latter. Some chemicals such as picric acid, nitric acid and "tetral" may cause yellow stains on exposed surfaces.

Some local discolorations may be of high diagnostic significance. Cullen's sign is a discoloration resembling a bruise at the umbilical region; it indicates intraperitoneal hemorrhage. Grey-Turner's sign, a localized pigmentation on the umbilicus or the loins, is of value in the diagnosis of acute hemorrhagic pancreatitis.

Melanin produces a localized or generalized brownish discoloration. This may be caused by radiation (sunlight, ultraviolet rays, roentgen rays), mechanical friction, or previous inflammation. Pigmentation may be observed in vitamin A and C deficiencies and in pellagra. Pigmentation is often encountered in endocrine disorders such as acromegaly, Cushing's syndrome and hyperthyroidism. The pigmentation of Addison's disease is of great diagnostic importance. It is most noticeable in the regions normally pigmented or exposed to light and pressure. In addition the mucous membranes of the mouth, conjunctiva and vagina are almost always affected. The color varies from grayish to brown with occasional minute black points.

The pigmentation of sprue is yellowish brown and appears on the face; sometimes it assumes a "butterfly" distribution on the nose and cheeks. Pigmentation is also seen in lymphoma. It may be generalized and either associated with erythroderma or independent of it. Acanthosis nigricans, manifested by a pigmented papillomatosis of the axillae and vulva, is of interest because of its high incidence of association with internal cancer.

The physician should acquaint himself with the normal variations of cutaneous texture. The most important are too dry (ichthyotic) and too oily (seborrheic). Each of these predisposes to a variety of disorders of the skin.

The texture of the skin is also affected by excessive perspiration. Nervous individuals who perspire profusely on the hands and feet are prone to develop maceration of the horny layer and also of the skin between the toes; this predisposes them to fungus infections. This is especially noticeable in obese women, who often develop intertrigo and moniliasis in the groins and under the breast because of excessive perspiration and friction.

Systemic conditions affect the texture of the skin. In iron-deficiency anemia the skin may be dry, inelastic and wrinkled. It is dry and delicate in pernicious anemia. It is sclerodermatous in some vascular disorders, especially of the extremities. Endocrine disorders also may affect the texture of the skin which becomes thickened in myxedema and thin and stretched in Cushing's syndrome.

Follicular hyperkeratosis gives the skin a rough sandpaper feeling; this is seen in keratosis pilaris and avitaminosis A.

Nails. Close observation of the nails may yield valuable information about the patient's health, habits and disease. Their shape, texture, color are significant; thickening, discoloration and irregularities should be noted. The care of the nails also gives a hint as to the personality of the individual.

It takes from four to six months for a nail to grow from base to free edge. Alterations caused by sudden change in the nutritional condition of the nail tend to manifest themselves as transverse ridges of the nail plate (Beau's lines). Therefore by examining a patient who presents these alterations in all

the fingernails, it may be possible to determine, by the location of the change in the nail plate, when the systemic affection occurred. Beau's lines develop after infectious disease, such as influenza, mumps, diphtheria, erysipelas, and high fevers of various kinds. Endocrine disturbances and vitamin deficiencies may also affect the growth and texture of the nails.

Some occupations which require constant immersion of the hands in soapy water or the handling of certain substances affect the nails and the tissue around them. Paronychia is common in bartenders, bakers, cooks and dishwashers. Discolorations are found in photographers and cigarmakers. Those who handle chrome salts develop ochre pigmentation; silver workers may show a slate blue discoloration. Picric acid makes yellow stains.

Some skin diseases produce other characteristic changes in nails. Fungus infections cause a yellowish thickening which starts at the distal end. Psoriasis causes multiple punctiform depressions and yellowish thickening. Spoon-nail may be seen in some anemias, especially in the iron-deficiency type.

Hair. Observation of the state of cleanliness and neatness of the hair gives considerable insight into the personality of the individual.

The rate of growth of each individual hair varies with age. When the hair reaches the level of the skin it grows from two to five mm every ten days, or about three-fourths of an inch per month. This can be noticed readily in persons who have stopped dyeing their hair and show the white color at the proximal end of the hairs. The rate of growth is affected by general health, the condition of endocrine system and by nutrition.

The use of hair dyes, hair-straighteners, hair tonics and brilliantine may cause a variety of cutaneous disorders, chiefly in the scalp, forehead and face. The hair may assume a dull and lifeless appearance in diseases of the scalp and also in systemic disorders such as endocrinopathies, *e.g.*, myxedema. Diffuse loss of hair without disease of the scalp may follow febrile diseases, major operations, childbirth, miscarriage, and excessive administration of vitamin A.

When the hair is observed the scalp should also be inspected. Items to be noticed include texture, presence of dryness or oiliness, the presence of scaly patches, diffuse or localized, the existence of bald spots where the skin is atrophic or of normal appearance; each of these characteristics has its own diagnostic value. Observation of the way the hair is combed may be also helpful. Straight-back hairdo may cause alopecia of the hairline on the forehead and on the temples, a result of constant traction. Exaggerated brushing of the hair and the use of some types of large roller have been reported to cause local alopecia.

Mucous membranes. Examination of a patient is not completed until the mucous membranes have been inspected. The observer should familiarize himself with the normal variations of color and texture of the mucous membranes caused by age and race. In older persons the mucous membranes of the mouth and genitals assume a pale color. In dark-skinned persons there are irregular patches of pigmentation on the mucous membranes of the cheeks. The local changes caused by friction of dentures, damage of ragged teeth, or biting of the

cheeks should be recognized. Harmless conditions such as Fordyce's disease, manifested by tiny pin-point to pinhead sized yellowish elevations, should be recorded but not stressed.

Some diseases of the skin are often accompanied by lesions of the mucous membranes of the mouth; their presence is helpful in the diagnosis. In pemphigus, bullae may be found, although usually these break easily and only an erosion is observed. In lichen planus there are typical white net-lace streaks not only on the cheeks and tongue but also on the glans penis.

The tongue may be affected by many local and systemic conditions. Well known are the "strawberry" changes of scarlet fever, the bright red, smooth atrophic tongue of pernicious anemia, and the glazed tongue of iron-deficiency anemia. The presence of fissures, leukoplakic areas, and ulcerations should be carefully noted.

When the oral mucosae are examined, the appearance of the teeth should be noticed, as this helps in the general inventory of the patient. The condition of the teeth and gums, the presence of pyorrhea, or infected tonsils may indicate the possible existence of foci of infection.

Examination of the mucous membranes of the genitals and anus should be performed as many conditions have typical manifestations in these areas. The penis is often affected by lichen planus, psoriasis, herpes simplex and the venereal diseases. The vulva is often affected by lichen sclerosus et atrophicus.

OBSERVATION OF THE DERMATOSIS

The analysis of the character of a dermatosis is made in two successive steps:

1) The determination of the primary or secondary lesions which form the dermatosis;

2) The study of the clinical peculiarities of the lesions, their location, number and distribution.

The human skin can react to insult, whether external or internal, in a very limited number of ways. These are called primary lesions. The characteristic of the primary lesions is that they appear without having been preceded by any other visible lesion. They are: macules, papules, vesicles, bullae, pustules, nodules and tumors. Secondary lesions are those that follow another cutaneous alteration. These are: scale, crust, excoriation, fissure, ulcer, scar and atrophy. These lesions are the alphabet of dermatology, and it is essential for the physician to know the exact meaning of the technical terms and the definition of each kind of primary and secondary lesion.

Primary Lesions

Macule: Circumscribed alteration in color of the skin, not appreciably raised above or depressed below the surface.

Papule: Circumscribed solid elevation of the skin; from the size of a pin-head to that of a split pea.

Nodule: Circumscribed solid elevation of the skin; from split pea to cherry.

Tumor: Circumscribed swelling larger than a cherry.

Vesicle: Circumscribed elevation of the epidermis; from pinhead to split pea; contains clear or non-purulent opaque fluid.

Bulla: Circumscribed elevation of the epidermis; from split pea to finger-nail in size; contains serum, or blood.

Pustule: Circumscribed elevation of the epidermis; from pinhead to finger-nail; contains pus.

Wheal: Circumscribed edematous elevation of the skin; evanescent.

Secondary Lesions

Scale: Dry, laminated exfoliation of the epidermis.

Crust: Dried exudation or secretion upon the skin.

Excoriation: Superficial solution of continuity in skin due to trauma.

Fissure: Linear solution of continuity; usually the seat of infiltration.

Erosion: Solution of continuity of skin involving loss of substance of epidermis down to upper cutis.

Ulcer: Solution of continuity of skin involving loss of substance extending into the cutis or deeper structures.

Scar: New formation of connective tissue, replacing loss of substance which involves cutis or deeper structures.

Atrophy: Decrease in number or volume of the elements that constitute the skin.

Macules: Macules are caused by: a) dilatation of the vessels of the corium; b) extravasation of red cells or their pigment; c) increase, decrease or absence of the normal pigment of the skin; d) deposit of foreign colorants or abnormal pigments in the dermis. A macule may be of any size and any color. Large macules pass into patches either by enlargement or confluence. They may be sealy as in pityriasis versicolor, but heavy scales usually indicate papules.

Macules may be round. When they are discrete their margins are sharply defined; when confluent the margins are often ill-defined, irregular or angular.

Macules may be localized or generalized, discrete or confluent, scanty or abundant. Their course may be evanescent, persistent or permanent. They may or may not be accompanied or preceded by subjective symptoms such as burning or itching.

The different types of macules include: a) roseola; b) erythema of confluent roseola; c) halo or areola; d) petechia, a circumscribed hemorrhage into the skin; e) ecchymosis, a larger hemorrhage, usually traumatic. Petechiae and ecchymoses do not disappear under pressure.

Papules: Papules may be caused by acute or chronic inflammation, by hypertrophy or by new growth. Their bases may be circular, polygonal or angular. The summits may be acuminate or pointed, round, flat, or umbilicated. The body may be sessile if the base is wide and flat, and pedunculated if the base is contracted.

The color of papules varies and may be of diagnostic value. It is whitish in

milium, yellowish in xanthoma, copper-red in syphilis, violaceous in lichen planus and translucent in cutaneous amyloidosis. The consistence may be boggy, doughy, soft, or stony.

In their distribution papules may be localized or generalized, profuse or scanty. They may remain isolated or form plaques or lichenification. They may develop into single straight lines (Koebner's phenomenon) usually due to the appearance of lesions on a scratch line, as in psoriasis, lichen planus and flat warts. They may coalesce and form rings, as the annular lesions of granuloma annulare, lichen planus and secondary syphilis. Papules may be grouped like a bouquet of flowers, as in corymbose secondary syphilis.

Among the clinical varieties of papules, we find: a) acuminate or pointed papules, such as those of pityriasis rubra pilaris; b) rounded, as those of erythema multiforme or secondary syphilis; c) flat-topped, as those of lichen planus; d) umbilicated, as seen in molluscum contagiosum.

Papules are of great diagnostic significance, hence their correct identification is important.

Nodules: Nodules differ from papules in that they are larger and deeper. They are usually located in the deeper portions of the corium and the subcutaneous tissue. At times they are slightly elevated above the level of the skin. They may undergo necrosis, ulceration, and cicatrization. The ulcerative type of nodule is often called gumma. Nodules are occasionally painful to the touch, as in erythema nodosum, but in most instances they are painless. They are usually manifestations of systemic diseases, such as syphilis, leprosy, lymphoma, deep fungus infections, tuberculosis, and sarcoid.

Tumors: Tumors are new growths of larger size than a nodule, composed by any of the structures of the skin or subcutaneous tissue. In dermatology the term "tumor" does not imply malignancy. Tumors may be located within or beneath the skin, or may be attached to it. Some may ulcerate. They are common in carcinomas, lymphomas and fibromas.

Wheals: Wheals are circumscribed edematous lesions which appear and disappear rapidly. They are characteristic of urticaria. Although usually small, they may form large plaques by confluence.

Vesicles: Vesicles are always located at the epidermis. Their color depends upon the character of the contents, upon thickening of the covering wall and upon the degree of concomitant inflammation. They may be dull or glistening, translucent, yellowish when filled with serum, reddish or reddish-brown to black when filled with fresh or old blood. The content is usually spontaneously coagulable fluid of the type of blood plasma, plus a varying number of leukocytes and a few epidermal cells. When the content oozes out it coagulates to form crusts. Except for the vesicles of possible nevus origin such as lymphangiomas, vesicles are always associated with inflammation and the liquid they contain is always an exudate. Vesicles may differ in the amount of fluid they contain and thus may be tense or flaccid. They may be simple or grouped, and may appear on an apparently normal skin or an erythematous base. They are usually accompanied by symptoms such as pain, itching, burning.

The most important clinical varieties of vesicles are: a) impetigo type, with tendency to break easily and form crusts; b) the herpes simplex type, usually grouped, and arising from an erythematous base; c) herpes zoster type, similar but usually larger, with less tendency to break; d) eczema dermatitis type, thin walled, easily broken, pruritic; e) dyshidrosis-"ids" type, deep-seated, non-inflammatory, usually situated on the sides of the fingers and toes; f) the varicella type, fragile and umbilicated.

The detection of vesicles is often of great diagnostic importance. They should be sought, if necessary with a magnifying glass, at the periphery of the lesions. Some diseases are never vesicular, such as syphilis and the cutaneous granulomas.

Pustules: Pustules are inflammatory collections of pus; they may arise from papules, vesicles or may appear directly as pustules. They may be follicular. They vary in size, shape and degree of infiltration. Superficial pustules are secondarily infected vesicles and are the direct result of infection, such as the pustules of impetigo of Boeckhardt; these heal without scarring. Deeper pustules such as those of pustular acne, syphilis and variola, are dermic, have more infiltration, and leave scars when they heal.

Pustules may develop in diseases of different etiology: a) pyodermas, primary or secondary to a vesicular dermatitis; b) acute infectious diseases, varicella, vaccinia, variola; c) some chronic infectious diseases, such as syphilis, tuberculosis, mycosis; d) some drug eruptions, such as bromides or iodides; e) as a result of contact with oils and tars; f) as a result of focal infections, such as pustular bacterid; g) some dermatoses of unknown etiology, such as pustular psoriasis and subcorneal pustulosis.

Bullae: These are large blisters, which may be filled with serum or blood. They may be tense or flaccid and may or not may have an erythematous halo. Bullae may originate within the epidermis, usually by acantholysis, as in pemphigus. Alternatively the top of the bulla may be formed by the whole epidermis, the fluid accumulating between the epidermis and the dermis, as in erythema multiforme. When a bulla has been opened it may leave an erosive area which may heal rapidly as in bullous impetigo, or slowly as in pemphigus. The liquid may dry up and form crusts, or the area may proliferate and form vegetations as in pemphigus vegetans.

Bullae may be caused by a) external agents such as trauma, burns and frostbite; b) local infections such as impetigo and erysipelas; c) systemic diseases such as leprosy, syphilis (only in the bullous syphilid of the newborn); d) drug eruptions, especially on the genitals and mouth; e) neurologic diseases such as syringomyelia and neuritis; f) diseases of unknown etiology as pemphigus, epidermolysis, and bullous erythema multiforme.

Bullae are always present in only two diseases: epidermolysis bullosa and pemphigus.

Scales: Scales are the normal end result of the keratinization cycle of the basal layer of the epidermis. The normal skin is constantly sealing, although in imperceptible amounts. Pathologic desquamation is the result of defective

cornification. Erythema almost invariably leads to desquamation. Desquamation follows inflammatory processes in which cellular infiltration is present. Edema of the corium alone does not lead to desquamation as it does not impede the nutrition of the cells enough to interfere with keratinization. Therefore urticaria is not followed by desquamation, while sunburn is.

Scales vary in moisture and fat content, in cohesiveness, adhesiveness and color. In psoriasis they are silvery and dry; in seborrheic dermatitis they are greasier and grayish, as they are scales-crusts with dry serum between the layers of the horny cells. Scales may be very adherent or may be loosely attached. The fine powdery scales of pityriasis versicolor and of pityriasis alba are hardly visible and can only be demonstrated by gentle stroking or scratching with a sharp object. The scale of discoid lupus erythematosus may present follicular plugs on the surface in contact with the skin, where the scale penetrates the follicles.

Crusts: Crusts are dried exudation or secretion upon the skin and may consist of serum, pus, blood or a mixture of the three. The presence of blood indicates destruction or denudation of the corium. Crusts should be pressed upon to see what exudes from the edges. A part or all should be removed in order to expose what is underneath. Crusts should be differentiated from scales and from necrosis.

Excoriations: Excoriations are traumatic lesions caused by scratching and are therefore common in pruritic eruptions. They are usually epidermal and do not result in scars but they often leave pigmentation which may persist for a long time. They are usually punctate or linear. Oozing of serum or blood may result in the formation of crusts. Excoriations often take a parallel arrangement when several fingernails have been used simultaneously in scratching. The presence of excoriation indicates that a lesion is pruritic.

Fissures: A fissure is a crack in the skin which occurs when the skin has lost its elasticity and expansibility through infiltration and thickening. Fissures are due to bending or other movements common in the natural folds of the skin as in the corners of the mouth, palms, soles, phalangeal flexures and anal region. Fissures are usually painful and may furnish the portal of entry for infection.

Erosions: Erosions are usually due to the breaking down of a primary lesion such as a vesicle, bulla, or pustule. They heal without leaving scars since they do not involve the corium.

Ulcers: An ulcer is an area in which the skin has been destroyed down to the corium. Ulcers which heal always leave scars.

Ulcers may be primary: a) caused by physical agents (heat, cold, electricity, x-rays, radium); b) chemical agents (caustics); c) infectious agents (chancre, TB ulcer); d) trophic changes, plantar ulcers.

Ulcers may be secondary to another process: a) breaking down of gummas and nodules; b) neoplastic diseases, blood dyscrasia; c) gangrene.

The following characteristics should always be noted in an ulcer: 1) location; 2) configuration (round or oval; serpiginous in phagedenic ulcers; geo-

metric or angular in factitial; annular or circinate in syphilis); 3) borders, flat or regular, undermined as in chaneroid, punched out, rolled, pearly (carcinoma), soft, hard; 4) base, soft, even, uneven, firm, flat, granulating, purulent; 5) discharge, serous, seropurulent, bloody; 6) color, bright red, livid; 7) surroundings, inflammatory edema, fibrosis, nodules, varicosities, etc.; 8) subjective symptoms, pain, burning, etc.; 9) condition of the related lymph nodes.

Scars: Scars are the record left by a destructive process. Study their distribution, configuration (arcs or segments or circles), color (new scars are pink, older ones are white), texture (thin, soft, wrinkled, thick, keloidal as in burns, tuberculosis), contractibility or mutilation (in TB, mycotic granulomas), fixation to underlying tissues. Secondary changes are scaling and ulcerative breakdown.

The relation of scars to the active process is important. In syphilis, the scar is left behind as the disease progresses at the periphery. In tuberculosis the scar may contain tubercles that break down and ulcerate.

CLINICAL PECULIARITIES OF THE ERUPTION

The study of the location of a dermatosis is extremely useful in its diagnosis. Even if the patient reports for examination of a single lesion, complete examination of the whole skin may reveal other lesions which are helpful in diagnosis.

An eruption may be generalized or localized, symmetrical or asymmetrical. It may follow a definite pattern, such as along a nerve distribution or it may have an apparently irregular pattern which nevertheless is characteristic of a disease. *Psoriasis*, for instance, has sites of predilection on the elbows, knees, scalp, nails, penis, and the upper part of the intergluteal fold. *Lichen planus* affects the flexor aspect of the wrist, the trunk, the penis, and the inner aspect of the buccal mucosa. *Seborrheic dermatitis* is found on the scalp, ears, neck, sides of the nose and the middle of the chest and back. *Atopic eczema* occurs on the face, especially the forehead, eyelids, and chin, also in the creases of the neck and the antecubital and popliteal spaces. *Rosacea* is distributed over the flush areas of the face, cheeks and chin, between the eyebrows, and on the tip of the nose. *Pityriasis rosea* is usually found on the trunk, along the lines of cleavage, sides of the neck, arms above the elbows, legs above the knees. *Erythema multiforme* affects the dorsa of the hands and feet, the sides of the neck and the mouth. *Acanthosis nigricans* is found at the axillae, sides of the neck. *Lupus erythematosus* affects the cheeks in a "butterfly" pattern.

A generalized dermatitis usually suggests a systemic cause, while a localized one is indicative of a local cause.

In the ever-increasing field of contact dermatitis the location of the eruption is an important feature. The uncovered parts of the body are exposed to external irritants or allergens. The face and dorsa of the hands are mostly affected by the actinic rays and therefore the sites of predilection on diseases in which this factor is important such as lupus erythematosus, polymorphous light eruptions and pellagra.

Contract dermatitis limited to some definite part of the body suggests definite etiologic factors. When restricted to the forehead it is indicative of hat-band dermatitis; if spread across the wrist it incriminates the metal or leather of a wristwatch band; on the dorsa of the foot it directs suspicion to some component of the shoe. Hair dye dermatitis often affects the forehead and eyelids. Toothpastes may cause dermatitis about the mouth.

The number of lesions is variable in the different conditions. Cutaneous carcinoma is usually single, while the tumors of lymphoblastoma are often multiple. Primary syphilis is usually single; chaneroid is often multiple.

Lesions may be isolated or grouped. In the latter case they may be annular, arciform, polycyclic or linear. A round lesion, coin shaped or nummular, is characteristic of psoriasis, nummular eczema and erythema multiforme. Oval lesions are seen in pityriasis rosea. Annular lesions with clear centers are characteristic of ringworm. Sometimes a ring is not complete and arciform lesions are produced; these are seen in syphilis, lichen planus and mycosis fungoides.

Occasionally the lesions are grouped irregularly but present a geographic pattern, with clear skin within the patches. This is often seen in psoriasis, pityriasis rubra pilaris and mycosis fungoides.

By confluence the lesions may form large patches, which may present a somewhat different picture than the individual lesions. In lichen planus, for instance, the grouping of papules form patches of lichenification, while at the periphery individual papules with the typical violaceous color and configuration may be found.

SUMMARY AND CONCLUSIONS

Much valuable information can be gained by careful observation of the skin, hair, nails and mucous membranes of the patient who has a dermatosis.

The patient should be observed first as a whole. An inventory of his general health, hygiene, occupation, age, sex, race and national origin may yield valuable hints as to the diagnosis.

The skin disease should be first examined from a distance, to note its location and configuration. The whole body should be examined, including the mucous membranes of the mouth and genitals, and palms and soles.

After a general observation of the eruption, a close observation should determine the primary lesion and the secondary one.

In dermatology it is best to avoid hasty diagnoses. A methodical, step-by-step approach will lead to a few possibilities to be considered. From there on the final diagnosis may be reached by laboratory tests, therapeutic tests, the course of the eruption, etc. It is always better to delay the diagnosis for a while than to make the wrong one.

On the Psychology of Medical Observation

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"To these fundamental laws leads no logical method, but only intuition, based on the empathic grasp of experience."

Albert Einstein, *Motive des Forschens* (1918)

It has been said that teaching in psychiatry on a graduate or postgraduate level all too often has consisted of redundant reminders of "how much good just listening does for our patients" (1). But if the patients are truly to benefit, the medical practitioner—or, preferably, the medical student—must be taught how to do much more. He must learn how to observe, how to evaluate his patients' remarks, and how to detect relevant cues among the data picked up while taking a history.

Indeed, medical observation should start when the patient first enters the doctor's office, with an inspection of the patient's attire, grooming and demeanor. Much is revealed by these factors alone, these aspects of nonverbal communication. The young woman who is dressed in drab colors and in clothes that don't seem to belong to her, whose hair style indicates she does not care about her appearance, who enters the consultation room without bothering to close the door and then sits down opposite the doctor without looking at him—this patient communicates aloofness and a feeling of alienation from her environment even before she utters a single word. While taking a history, the physician may direct his questions toward eliciting specific information about the possible loss of a love object or about any other experiences that might be responsible for triggering a depression; he will also do well to find out whether his patient feels estranged from her family and friends and gives evidence of depersonalization and withdrawal from her environment. The all-important issue is that he refrain from jumping to rash diagnostic conclusions and firmly keep in mind the relevant associative cues.

Merely to observe the obvious and to indulge in common sense conclusions will result in erroneous assessments and in alienating the patient, who will feel dissatisfied that his doctor has not bothered to try a bit harder to understand him. A case in point concerns a psychiatrist who developed a serious otitis media in his left ear. While being examined by a competent ear, nose, and throat specialist, he was reassured about the mild nature of the trouble, the absence of any significant hearing loss, and the advisability of conservative treatment. Then came a brief discussion regarding the length of treatment and the possibility of a recurrence. The psychiatrist remarked that the accumu-

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lation of fluid in the middle ear created an uncomfortable sensation of pressure and fullness and impaired his perception of his own voice. A week later, during the second consultation, it was apparent that the condition had not completely cleared up. The psychiatrist was again reassured about the prognosis and told to be patient. At this point, the ear, nose, and throat specialist asked: "Do you mind if I mention your case in my next lecture to residents? I want to teach them the significance of the total life and work situation in the individual patient's reaction to even the mildest pathology. It is obvious that you are especially concerned about your ear infection because as a psychoanalyst your left ear is of particular importance to you, sitting as you do behind the patient who lies on the couch to your left, no doubt. No wonder even the slightest hearing loss in that ear causes you anxiety."

So plausible did this explanation seem to the specialist (and would it have seemed to his residents) that it precluded any exploration of the true circumstances. The doctor, satisfied with his glib interpretation, felt it unnecessary to ask his patient such pertinent questions as: "What does this ear trouble mean to you? Have you had any ear infections in the past? Has anybody else in your family ever had trouble with his ears?" These simple inquiries would have revealed to the specialist that the psychiatrist's only brother had developed a chronic otitis media in the left ear as a young boy and had been treated conservatively for years by a prominent specialist whose opposition to surgery was well known. Eventually the boy had developed a cholesteatoma in the left mastoid process and died of sinus thrombosis and septicemia. It would have been easy to elicit these most relevant data in five to ten minutes. Moreover, the location of the psychiatrist's couch could hardly be relied on to give a deeper understanding of the patient's anxiety concerning the infection in his left ear. Roughly 60 per cent of his patients usually faced him while seated on a chair; less than half made use of a couch, which was located on the doctor's right.

Conversely, the doctor must be able to observe his *own* emotional reactions upon being exposed to a patient's problems. This was vividly demonstrated in a group discussion in one of our postgraduate seminars in psychiatry for physicians conducted at The Mount Sinai Hospital (2). The subject under consideration was how much to tell the family about the seriousness and nature of the psychiatric illness of one of its members. Suddenly a doctor took the floor to pose an example. A schizophrenic patient of his had been institutionalized, and her twelve-year-old son had asked whether he, too, might become mentally ill. The psychological factors motivating the boy were explained to the doctor, and he was advised that the boy should have been reassured that, to the best of present knowledge, schizophrenia is not hereditary and that his mother's illness in no way affected his outlook for mental health. At this, the doctor interrupted excitedly: "All right. So much for soft-soaping the boy. Now what about the truth?" Some time later we learned the reason for the doctor's agitation: his brother had been in a mental institution for years.

To understand a patient's emotional suffering, the medical practitioner

must go beyond establishing a correct diagnosis of somatic illness. He must elicit from the patient what motivated the timing for a checkup or what it means to him at this particular stage in his life to be afflicted with this illness or traumatic injury to his body. How much more understanding of "the total life situation" and contributing emotional factors does the physician gain who, in the course of a physical examination, routinely asks his patients: "Why do you come to me at this time? You have had this complaint before, haven't you?"

It is of particular significance that the postgraduate student of psychiatry often expresses surprise and disbelief when confronted by instruction that emphasizes the importance of proper handling of the doctor-patient relationship based on efforts to understand the patient as a human being motivated by fears, by anger, by love and hate and by many other inner needs (2). Fragmentation of medicine into an ever increasing number of separate specialties and subspecialties has increased the danger of dehumanization in modern medicine. The medical specialist as a highly trained technician concerned only with a specific organ system or body part, not with a human being suffering pain and anguish, is one aspect of the problem, but only one. The contribution of modern psychiatry to the education of the physician is recognized (3), the changes in the medical curriculum in the past twenty years are widely discussed, the literature on the importance of the role of the medical practitioner in the emotional reactions of his patients is immense (2 to 8), but the finished product, the young physician, the medical intern and resident, show a truly astonishing disinclination to heed the emotional alarm signals their patients are giving off. General practitioners who have attended postgraduate courses in psychiatry at The Mount Sinai Hospital during the past five years, some of whom were relatively recent graduates of various medical schools in the country, agreed that the many subtle aspects of the doctor-patient relationship had not been stressed sufficiently during their years of training. This tends to confirm the findings of Shumacher and Gee (9) for doctors of the 1950 graduating class, who for the most part stated that this was indeed a major deficiency in their training, and of Kaufman (10) who has observed that "of all the subjects that the intern has been exposed to as a medical student he shows the greatest ignorance in the field of psychiatry. He may know the lyrics but he cannot carry the tune."

In our experience in teaching postgraduate psychiatry to medical practitioners at The Mount Sinai Hospital, we have learned that the doctor who relies heavily on the time-worn clichés and expressions is usually the one most prone to be blocked when it comes to observing his patients' behavior and to interpreting what he sees. It is not enough to state: "This patient is tense and anxious," and to prescribe one among a number of tranquilizers, or to say: "The patient is depressed and anxious," and to prescribe a tranquilizer combined with an antidepressant drug.

It is quite true that the patient who is expecting her fourth child at a point in her life when her three children need her much less than before and when

she had already decided to resume an academic career interrupted by the birth of her first child may well be tense and anxious. But to tell her that and to offer her a tranquilizer will accomplish much less for her than to give her an opportunity to verbalize her disappointment over the need for postponement and to help her face up to her anger without mobilizing excessive guilt feelings. She can be made to see in very brief talks that there is no need to give up her integrity as an individual with well-defined goals and ambitions because of her pregnancy and the demands of a new child on her time and energy. But to tell such a woman that she is "tense and anxious" often has just the opposite effect from the one intended by the physician; the woman interprets these terms as a reproach by the stern father substitute and feels guilty about having had any misgivings or regrets about the timing of her pregnancy. Medical terms that have become labels eventually lose their usefulness and may become harmful. The toxic effect of certain fixed expressions, when used in front of a patient during grand rounds or in the privacy of the doctor's consultation room, is well-known to psychiatrists. Just as in scientific research progress at a given point may depend on finding an adequate new language to express and communicate new developments and advances, so must the physician learn to reach his patients through a manner of speaking that meets their needs.

The old body-mind dualism is still alive in many physicians today and is responsible for a "partisan" attitude, be it purely somatic, exclusively psychogenic and environmental or rigidly genetic. It would appear, therefore, that we need a much wider consensus among physicians that a comprehensive approach, a monistic point of view, is the one that alone does justice to our empirical data. But attitudes are not changed by exhortation nor by logical remonstrance alone. The physician who is handicapped by a deeply ingrained conviction that organic illness precludes emotional conflict and that an emotional or "functional" disturbance can be only considered after repeated examinations and laboratory tests have failed to produce evidence of organic pathology—that physician treats organ systems rather than human beings. He has remained deaf to his patients' verbal and nonverbal signals and symbolic expressions of emotional conflict.

What is the reason for such an attitude? Is it due to powerful inner resistances by the medical student to an area that is deeply disturbing because it deals with the unconscious and with instinctual forces that he regards as potential threats to his detached, "objective" professional attitude? There is more and more supporting evidence for the impression that many physicians begin their internship with a hostile and cynically rejecting attitude toward anything pertaining to the emotional life of the patient. These same physicians not infrequently reveal a remarkably "partisan" attitude concerning their specialty, diagnostic conclusions, ways of medical reasoning, in short, their "scientific method," while pointing out that psychiatry is not yet an objective science and psychological medicine is still too widely open to each individual examiner's interpretations. These old objections are still voiced by physicians

who believe that they are scientists endowed with a scientific mind and trained in the objectively proved ways of applying the scientific method in the examination of all their patients. Some physicians seem almost obsessed by what has been called "*the fetishism of the single cause*" (11) and utterly unable to accept the fundamental tenet that psychopathology can, and often does, co-exist with organic findings. The search for the one big secret of nature to be unlocked by discovering the right formula, by applying the correct model of thinking, has vexed natural scientists and philosophers alike. Physicians must be made to realize that such a simplistic pursuit of obtaining mastery over complex interacting forces is rooted in unresolved infantile strivings for omnipotence rather than in sound medical observation.

We have been impressed for some time with the prevalence of rescue fantasies as an unconscious motive in the choice of medicine as a profession. Those who have had an opportunity for psychiatric and psychoanalytic exploration of creative artists as well as scientists are struck by certain similarities in the dominant psychological mechanisms. It would appear that all creative endeavor is intimately related to the aggressive instinct and that artistic creation as well as scientific pursuit of discovery are restitutive processes based on an unconscious need to produce something of enduring value—"goodness and wholeness from that which in fantasy had been injured and rendered bad" (12). It is at this particular point that the physician comes closest to embracing the functions of both the scientist and the artist because healing, like artistic creation, is magic. Artist and healer alike strive for mastery of destructive forces through control. The more perfect such control, the more widely applicable the new law and order brought into the wealth of threatening phenomena, the greater the scientist's, the physician's as well as the artist's success. Lack of mastery produces anxiety and helplessness. This would explain the ready acceptance of theories in medicine in those areas where we feel most threatened by uncertainty and lack of real understanding. It would seem that even an unsatisfactory theory alleviates the horror vacui.

Each generation feels the many threats to human existence as keenly as the preceding one and reacts very much like the manic-depressive patient who has had many recurrent depressions during his lifetime but who is convinced that the current depression is the worst one he ever experienced. Since the means and ways in which human existence is threatened take on new aspects from time to time, man is only too ready to believe that the new threats to his survival are more destructive, more frightening than past dangers, but the history of medicine and particularly the history of medical psychology teaches us, if anything, that over the centuries man has always felt surrounded by inimical forces and forever searched for "basic security," that elusive goal.

Too many physicians unhesitatingly accept the clichés about the "global anxiety of our time" and "the understandable world tensions of the nuclear era" that are responsible for the age of anxiety in which we live. "The atom, the indivisible and most basic particle of matter, has been split and brought to disintegration," writes Sterba, and "the basic insecurity of our time is not in

the least a result of this scientific disintegration of our world concept" (13). But world concepts have been challenged and undergone changes in each successive generation, always presenting threats to the quest for security and stability. Progress inevitably leads to change and change necessitates re-orientation and renewed efforts for adaptation. Change, brought about by science or art, threatens the established order and thus produces anxiety and anger. Jaspers, a leading exponent of existentialist philosophy and psychiatry, has also raised his voice in warning against the threat of destruction through nuclear energy. It is significant, however, to find that as early as 1930 Jaspers saw the individual in our era threatened by three destructive forces: modern technology, the Marxist doctrine, and Freud's instinct theory (14).

A trend established by advances in medical research in any given era may become dogma. Medical dogma combined with the forceful personality of a great teacher can produce a barrier against independent observation and research. In the writings of Hippocrates, we find stressed the importance of careful inspection of each individual patient and the great variability in manifestations of the same disease. In the case of tuberculosis, for instance, Hippocrates was pointing in the direction of the ecology of disease, taking into account such factors as changes in climate, the geographical origin of the patient, his age, race, and general constitution. By prognosticating on the basis of environmental and many other factors, he avoided narrow categorical statements based on the nature of the diagnostic entity alone.

Interestingly, Hippocrates was the first teacher in medicine to record his failures in medical practice. He pointed out that we learn much from recording our mistakes rather than our successes in practice.

His most astounding achievement was to free the medical practice of his time from the domination of theology and philosophical speculation, and to replace them with the new empiricism of medical observation. On rereading the writings of Hippocrates, one is struck by the truth that, in order to observe and report accurately and relevantly, the physician must be able to ignore the idols of the market place, the fashionable trends that may represent the most superficial aspects of the mentality of his era.

The Hippocratic method was held in high esteem, but it is an ironical fact that this high regard eventually proved its undoing: his classic forty-two clinical case studies gradually became exercises in memorization rather than instructions in precepts and orientation. His flexibility of mind and keenness of perception were lost in a slavish adherence to "the text."

Galen's writing later suffered a similar fate. For centuries the practicing physician adopted the attitude that if his findings did not correspond to descriptions found in his classic text, then "nature has erred because Galen cannot be in error."

The prevalence of unrealistic ideas concerning scientific observations is startling. A most widely cherished notion is that the dedicated student with a solid foundation of knowledge, the best training available, and a coldly logical mind, is totally equipped to add to man's understanding of nature.

The classical scholar and humanist Gilbert Murray perceived the true complexity of the creative process when he said: "The uncharted surrounds us on every side and we must needs have some relation towards it, a relation which will depend on the general discipline of a man's mind and the bias of his whole character. As far as knowledge and conscious reason will go, we should follow resolutely their austere guidance. When they cease, as cease they must, we must use as best we can those fainter powers of apprehension and surmise and sensitiveness by which, after all, most high truth has been reached..." (15).

One can only be amused by the evidence of this great humanist's own bias toward the power of the dynamic unconscious by relegating it to a secondary position. Here Gilbert Murray erred. The uncharted regions of the human mind referred to are all the manifold unconscious motivations and link-ups which act as invisible prompters off-stage. We do not have recourse to these unconscious resources after knowledge and conscious reason are exhausted. If we had to postulate a chronology of processes, the order would be reversed. Unconscious motives propel and direct our drives, channel our conscious thoughts and focus our interests. But the influence of these unconscious forces never ends; instead, it remains an ongoing process, concomitant with all conscious activity.

One is reminded of the certainty expressed by some of the great teachers in the exercise and application of logic to all the sciences, such as John Stuart Mill. "The business of inductive logic is to provide rules and models (such as the syllogism and its rules are for ratiocination) to which, if inductive arguments conform, those arguments are conclusive..." Mill seemed to regard deductive reasoning with condescension because it "merely expands and unfolds" natural laws and information already contained in the premises on which the researcher's work is based. And yet we find a consensus among scientists today to the effect that the inductive process "cannot achieve certainty... the only act which the scientist can execute with logical certainty is the repudiation of what is false" and "the formulation of a natural law begins as an imaginative exploit" (16).

Medawar's postulate was that "the idea of naïve or innocent observation is philosopher's make-believe" (16). How does scientific medical observation operate? It is of course true that we do not, "uncorrupted by prejudice or past experience, passively accept the imprint of sensory information from the outside world and in due course work it into complex notions... In all sensations we pick and choose, interpret, seek and impose order, and devise and test hypotheses about the nature of what we witness. Sense 'data' are taken, not merely given. Hebb has convinced us that we *learn* to perceive."

In 1883 Helmholtz gave a lecture aimed at answering those critics in the scientific world who accused him of having robbed Robert Mayer, the physician from Heilbronn, of his just claim for priority as discoverer of the law of conservation and transformation of energy (17). Robert Mayer published his paper in 1842. Helmholtz reported his extensive work on the same topic in

1847. Robert Mayer's priority is therefore established beyond a shadow of a doubt but Helmholtz, who was not a practicing physician but professor of physics and a man whose range of knowledge, ability as an imaginative experimenter and exact scientist and whose familiarity with the work of other leading researchers in the field were second to none, had paid no attention to the two short papers published by Mayer in 1842 and 1843 because the presentation of his ideas concerning the law of conservation of energy was "unsatisfactory." He offered no convincing experimental proof and furthermore, the introduction to his article might have discouraged a scientist from reading on because of his interpretation of the sentence "*causa aequal effectum*," cause equals effect, as meaning that that which is acting as cause is indestructible. There were easily detectable mistakes in some of the few calculations contained in this historic publication. The astonishing fact remains that in spite of scant material presented, vitiated by repeated errors in calculation and interpretation, and cloudy generalities of doubtful value, Robert Mayer arrived at correct conclusions and obviously had correct ideas concerning the law of conservation of energy. How was this possible? How had Robert Mayer arrived at one of the most revolutionary discoveries in science of our time, though lacking in scientific know-how and ability or perseverance and though heavily burdened by vague metaphysical notions? As Helmholtz has said, Mayer's method was largely inspirational and intuitive.

Robert Mayer was the youngest of three sons of a pharmacist who had awakened the boy's interest in natural sciences and medicine early in his life. In an autobiographical sketch Robert Mayer reports that "a frustrated attempt to construct a perpetuum mobile created a lasting impression in the 10 year old who busied himself with mechanical and chemical experiments . . . ; when he later as an adult realized the fundamental impossibility of what he had once attempted as a child, he had already laid the foundation for a correct theory of natural forces to which heat also belongs . . . Taught by his elders that he was in error since through the transfer from a big wheel to a smaller one as much energy is lost as velocity is gained, he quickly abandoned his project, but gained through his error in his early youth the insight that nothing comes from nothing." He became a ship's doctor as a young man of twenty-four and on a journey to the East Indies suffered a severe depressive episode. We find the following note in his diary dated April 10, 1840: "Somber thoughts, grave worries which focus on the sacred head of my father are pressing today, more than ever, upon my soul." An entry from his diary from the 30th of May reveals: "Father's birthday. Dark worries oppress me on this festive day which we had often passed happily in the family fold and only with effort was I eventually able to free myself." During the next week his depression cleared up to be replaced by a hypomanic reaction and Robert Mayer suddenly makes his epochal discovery (18).

Helmholtz and the history of science of the nineteenth century teach us an important lesson: a scientific observation, in medicine as in any other scientific field, to be recognized must be timely. It is quite evident that nobody would

have bothered with Robert Mayer's brief communications on the law of conservation of energy in 1842 and 1843, had it not been for the fact that K. F. Mohr had already published a treatise on the mechanical theory of heat in 1837, that Joule in England was working on experimental proof for the very same law at least since 1840 and that toward the end of the eighteenth and during the first half of the nineteenth century preoccupation with this scientific problem was far from unusual. In other words the solution to the problem culminating in a great discovery of a fundamental law of nature "was in the wind" at precisely that time when young Robert Mayer had his transcendental ideas which in psychic actuality were highly elaborated rationalizations for threatening unconscious aggressions directed against his father. The great Helmholtz knew something about that too. His own correspondence with his philosopher-father reveals his struggle over the years between the indomitable force, the inner necessity, to prove his father wrong and his often tortured attempts to retain the façade of the pious and respectful son. He was successful, though, in finding the substitute channel for this need by proving his illustrious teacher, the physiologist Johannes Müller, wrong. His admiration and respect for his teacher were boundless but as soon as he obtained his own laboratory and teaching position, he set out to prove with imaginative and extremely painstaking experiments that his former master was mistaken in asserting that it would never be possible and, indeed, a waste of time to ever attempt to measure the speed of transmission of the nerve impulse. Helmholtz succeeded in measuring it and insisted upon publication of his findings in Johannes Müller's own archives. It is also of more than passing interest that Johannes Müller had remained a "vitalist" who believed in a mysterious vital energy which is eventually used up and dissipated. Here again, Helmholtz proved his teacher wrong by establishing the principle of conservation of energy.

So much about unconscious motivating forces and their significance. But the two points Helmholtz alluded to in his lecture on the problem of Robert Mayer's priority are of equal importance (16).

1. The scientist, not unlike the artist, must speak a language intelligible to his contemporaries in order to find recognition. An idea that is expressed in vague terms without reference to a pre-existent body of knowledge may easily be overlooked.

An instructive example of this is the fate of Paracelsus' startling description of the working of the unconscious in children suffering from chorea which he gave in the beginning of the sixteenth century. In 1526 he wrote a slender volume entitled *Von der Krankheiten so natürlich der Vernunft berauben*, in which he asserts that children possess imagination and that chorea lasciva is due to imaginings and ideas. In children just as in adults "the cause is also imagination based not on thinking but on perceiving, because they have heard or seen something. The reason is this: their sight and hearing are so strong that *unconsciously they have fantasies* about what they have seen or heard." This appears to be the first mention of unconscious motivation of

neurosis in the history of medical psychology (19). This first accurate clinical reference to the role of the unconscious in medical literature was so completely cut off from the preoccupations and trends of scientific investigation in medicine of that period it found no echo of acceptance or recognition. In fact it was completely ignored for almost four centuries.

Michael Servetus is credited with one of the great discoveries in human anatomy and physiology, that of the pulmonary circulation. He described his findings with "extraordinary clearness and accuracy. But so little did he think of the discovery, of so trifling importance did it appear in comparison with the great task in hand of restoring Christianity, that he used it simply as an illustration when discussing the nature of the Holy Spirit in his work *Christi-anismi Restitutio*" (20).

2. There are powerful socio-psychological phenomena in back of seeming coincidences of simultaneous discovery of a law of nature by independent investigators who at times do not even know of each others' existence. It would appear that at a given time in history a scientific truth "wants out." This may be based on a whole gamut of cultural and emotional attitudes, developments and constellations which comprise the *Zeitgeist*. It has been said that even though there may be no awareness whatever of the spirit of the times in a creative individual, what matters is the fact that he is "subject to it." Once this push toward a new position in science, literature or the arts has resulted in explosive creative advances and discoveries, their repeated verbalization "becomes a new visible and living cultural force" (21) while their wholesale acceptance leads to many imitators. We may compare this latter phenomenon to an observation of psychotherapy: a correct interpretation may provoke a flood of confirmatory associations in the patient.

A most revealing statement made by Freud in his autobiographical study illustrates the point: "While I was writing my history of the psychoanalytic movement in 1914, there recurred to my mind some remarks that had been made to me by Breuer, Charcot, and Chrobak, which might have led me to this discovery earlier but at the time I heard them I did not understand what these authorities meant; indeed, they had told me more than they knew themselves or were prepared to defend. What I heard from them lay dormant and inactive in me, until the chance of my cathartic experiments brought it out as an apparently original discovery. Nor was I then aware that in deriving hysteria from sexuality I was going back to the very beginnings of medicine and following up a thought of Plato's" (22).

What makes a good physician? An aptitude for scientific research, a logical mind, a good grasp of scientific methodology and complete integrity as a researcher? All of these are important, but they are not enough. *Attitude* is even more important than encyclopedic knowledge and diagnostic skill. To speak and not merely to listen to his patients in a meaningful way and to understand some of the complexities of the doctor-patient relationship is equally important. The doctor will then be able to become exposed to his patients' emotional problems "without being affected by their upset and without

generating disturbing anxieties within himself" (2). The greater his ability to examine himself and to become aware of his own motivations and reactions, the better his chances to be attuned and responsive to his patients' overall needs.

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A Layman's Observations of Doctors

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New York, N. Y.

We—a family of three—are fussy about doctors.

This is so because of awareness of the irreparable might-have-been after jolting experiences.

Item: I was in an accident and suffered a basal skull fracture—seven bloody spinal taps, Weber's syndrome, papilledema. I was a mess. A surgeon wanted to trepan. A neurologist locked up the saw and threw away the key. I left the hospital with one bad result—fallen arches.

Item: My wife was working too hard, and the topside gears suddenly jammed. I insisted upon hearing the frightening possibilities: paranoia, schizophrenia and related psychoses. Psychiatrist A (and others) proposed a state institution. Psychiatrist B (and others) urged a nursing home. All the prognoses were dismal. The pressure for confinement was powerful. I consulted psychiatrist C. He arranged for hospitalization, ordered tranquilizers, advised patience. The combination worked. In a few weeks I took her to Honduras on a banana boat to change the scene, to substitute new ideas for old apprehensions. We have a very happy home.

Item: Our daughter had a congenital strabismus in one eye. When she was eight we consulted ophthalmologist A. He used the \$64 words of the medical dictionaries, lent us a book with \$98 words and recommended surgery, which he described as certain and corrective. Then he sent a contract requiring partial payment before he lifted a scalpel. In our concern, we agreed. Then, only then, he operated. When the bandages were removed, our daughter was walleyed. There had been too much of this, too little of that, he said, and he would have to cut again—for a duplicate fee. We didn't spin the plate with him again. We went to ophthalmologist B. He examined, tested, talked informatively. In a year he operated. Today our daughter's eyes are quite pleasing to the eyes of others.

These were awakening lessons, corroborated by other happenings over the years. The health, the happiness, perhaps the lives of each of us had been at stake. Why? Because education was incomplete. Or judgment was poor. Or empathy blinded. Or the fingers of skill blunted. Or misfits were in control.

Men of medicine were the vital factors in all these incidents in which blight brushed three lives. And men of medicine were the rescuers, repairing the mistakes of their colleagues.

Suppose there had been no appeal from the decisions of the inept. Would I be cataloging these events—or anything anywhere—if the surgeon had hacked at my head? Would my wife be nuzzling in my arms and delighting my palate and nudging my brain cells if she had been committed to an institution?

Would our daughter be a superior student and the popular companion of her classmates if she had been condemned to being a walleyed kid?

The answer to each is probably no.

This is scarcely a news flash—that all these doctors, the wrong and the right, were schooled in the same principles, privy to the same information, sworn to the same oath, licensed under the same requirements.

Why, then, the vast range of difference in their capabilities? Because they are human beings.

A host of doctors forget that, if they ever acknowledged it. Medicine has been cloaked in mysticism and mumbo jumbo for ages, and many physicians preen in the trappings. Ten times as many laymen find comfort in the delusion, preferring to believe the profession omniscient.

It isn't. And it has an extraordinary obligation. But doctors are human beings, subject to the frailties of the species. So what does one do when in the market for a doctor? One shops.

Unhappily, the task is not as simple as ordering a dry martini. What we—my family and I—want are doctors of competence, conscience, consideration, prudence and educated audacity. These attributes are all plus, of course, a dash of humor, the priceless ingredient of any human mixture.

Happily, we have what we want. But we didn't come by them easily. We had the good fortune to have the right man nearby when the wrong man blundered. We had the good sense to profit by experience, to learn that M.D. is not synonymous with magic, to seek advice, to examine credentials, to proceed with caution. We had the advantage of being in one of the world's great medical centers to make our choices. We had the price to pay.

The money wasn't always available. It wasn't asked, expected, or offered when I lay comatose, my spine punctured to relieve pressure, my veins pierced to receive caffeine, my intestines squeezed with Epsom salts. My second gift of life was free—and also my education in the ease with which a patient might slip to death on one doctor's word, or live on another's.

It happened in Bellevue Hospital, where I was sent only because a vigilant physician saw a trickle of blood in an ear and suspected a head injury. A surgeon wanted to operate. The late, great Foster Kennedy stayed his hand.

The night before I was to be released, after seven weeks, Dr. Kennedy stood at my bedside with a train or five or six students.

"Well, we didn't cut," he said, "and the prognosis is good. We'll never know what would have happened if we had operated. We do know what happened when we didn't."

And I know and shall never forget.

I hadn't given much thought to the difference in doctors before that, probably because I'd had no serious illness or injury. Then I undertook a survey in contrasts: Dr. Wrong versus Dr. Right.

Item: The symptom was a rash on the personal equipment most cherished by a man. It was a terrifying manifestation to someone with a little information—and on a Sunday. There was much reading of an encyclopedia and a

treatise on venereal disease. Lymph glands tender and swollen? Of course. The night was long, sleepless and bedeviled.

Dr. Wrong heard the story the next morning. He dusted rubber gloves, carefully fitted them, gingerly handled the member. His manner was cold, his movements hesitant, his words alarming: "It looks suspicious. You need a specialist."

Dr. Right was a busy dermatologist. The hour and a half wait was torture. What was on the pages of those magazines in his waiting room?

"Well, let's look at it," he said at last.

He took it in his bare hands.

"If that's syphilis," he said, "I'll treat you free."

He reached for a book, thumbed through it and showed a color plate.

"This is what you have," he said. "It's a cold sore, the same as on the lips."

He made a smear, went to another room and beckoned: "Here's a slide of your smear," pointing to a microscope, "and here's a slide of a spirochete."

This was a man who knew what he was talking about, and knew how to say what he knew.

To confirm his judgment, he took blood samples for analysis.

Item: The symptoms were nervousness, insomnia and backache. The patient explained to Dr. Wrong.

"It's probably menopause," he said.

"But I'm only thirty-seven," she said.

"That doesn't make any difference, it can be at any age," he said.

She left his office in tears. From him, no help, only new worry.

All right, so there's no timetable for menopause. But is a doctor privileged to offer a blunt, devastating opinion based on superficial information? Perhaps. A doctor is a human being.

But so is Dr. Right. He listened sympathetically to the patient's story. He made a physical examination. He prescribed a tranquilizer. His conclusion: "Forget it. Eat well. Don't stay up too late. There's no evidence of menopause and don't worry about it."

There have been other distressing incidents with doctors. But they have served as warnings, leading to discovery of the right doctors, and I like to think of those who have taken the time and had the interest to give a straight answer to a question, or make a point with drollery. These are things a patient remembers, such as:

On overweight: "All food is good, just don't eat too much of it. Take off five pounds now, and you won't have to worry about twenty-five later."

On whether a forty-year-old should bother with inoculation against polio: "If a bug comes and sits at the foot of your bed, it doesn't ask your age."

On the advisability of sex during recuperation from a head injury: "Just don't screw your head off."

On the long period of recovery from a severe foot injury: "There is nothing more I can do. Cells have to build. Remember, it takes nine months to make a baby, and there's no way to hurry the process."

On vitamins: "Americans spend millions of dollars every year on vitamins, and most of the money is a waste. The best food in the world is available to us, and it has everything we need for good health."

On impaired vision: "She'll never have fusion, so she can't pilot a plane or become a tennis star. So?"

On the prognosis after a siege of nervous exhaustion: "All you need now is TLC." "TLC?" "Tender loving care."

It is axiomatic that a doctor, by instinct and training, has much to contribute to human need. But his potential extends far beyond mastery of Gray's *Anatomy* and acquaintance with the products of the pharmaceutical houses. He can be friend and counselor, the Voice of Wisdom, and St. George against the dragons of insecurity.

For application of these roles to the individual patient, he must know the whole person. That, to my way of thinking, is paramount for maximum success in his ministrations: to know whether drinking is a problem, or smoking is a problem, or sex is a problem, or money is a problem, or work, or play, or the relationship of one family member to another.

Our doctors qualify, and when we go to them, we go with confidence.

Our twelve-year-old daughter epitomized our feeling not long ago when we were vacationing in the Caribbean. She developed a painful ear infection, and the local doctor prescribed antibiotic drops, which we learned later were contraindicated. The ache increased and she was in great discomfort. After three or four days, she said: "Can't we go home to our own doctors?"

We could and we did, because what she was saying was that she had faith in our doctors, which is what man needs in a doctor, which is what man needs in all his human relationships.

In Memoriam

PAUL KLEMPERER

1887-1964

It is not an easy task to pronounce the eulogy of a revered teacher. Yet if the result is to be truly worthy of its subject, it must be given as dispassionately and objectively as human frailty permits. And an objective statement is unquestionably what Dr. Paul Klemperer would have preferred.

In addition to the emotional relation which prevails between pupil and teacher there are what might be called the peculiarities of perspective. The junior assistant at the age of twenty-seven is assigned to the distinguished scientist who has reached the awesome age of forty-six and carries the orb and scepter of scientific eminence.

In later years the perspective changes. Carried away to other cities and other countries and immersed in the complex world outside the laboratory, the disciple discovers with astonishment that his work is still watched—critically and appreciatively and is endlessly encouraged.

The passage of additional decades brings a new phase and a new perspective. The elderly scholar, happy in his retirement, has devoted himself at last to the study of basic philosophical principles. He still finds time for his middle-aged disciple and in the seclusion of the library they discuss their research and debate moral problems. Time has changed their relation, enriching, strengthening and deepening it.

If a man in his time has played many parts, men in their times come to observe and appreciate many different aspects of those with whom they have been associated. It is for this reason that a man of large dimensions must have more than one eulogist.

The aspect of Dr. Klemperer which most often came to the fore during the three decades of our acquaintance was that of the scholar—the patient, meticulous, discriminating, unprejudiced analyst—who applied the riches of his mind at first to anatomical problems and later, with equal ability, to wider issues.

But scholarship, even when qualitatively unimpeachable, has been known at times to be afflicted with the vices of triviality and irrelevance. It was here that another of Dr. Klemperer's excellent traits flashed forth. He constantly tended toward basic principles, attempting to plumb the depth of each ocean that he traversed and charted.

This tendency toward profundity is well known to those who observed the steady progress which he made in the study of the diseases of collagen. It also



PAUL KLEMPERER, M.D.
1887-1964

explains his attitude toward pathology as a whole and it likewise describes his work as a medical historian.

He felt that pathology is the basic discipline of medicine and hence offers the truly fundamental approach to the understanding of disease. But a lifetime of laboratory observation had convinced him that in order to understand pathology in all its depth it was necessary to understand the nature of our concepts and this could only be achieved by a careful study of their development since classical antiquity. Thus the search for understanding brought him at last to the history of medicine, which he viewed as predominantly the study of the development of ideas. In this field he achieved and published enough to convince observers that his *opus magnum*, if he should complete it, would be a masterpiece.

Living as we do in an era when our circumstances, conditions, and habits are more and more altered by the increasing power of machines, we have all had occasion to reflect that although machines are increasingly imitative of the human intellect, there yet remains an important area in which they do not threaten our primacy. This is the realm of what we designate as our distinctive humanity. And this is the area in which Dr. Klemperer's excellence shone at its brightest. Sensitive and alert but not sentimental, he constantly sought to preserve the human and humane element in complex situations where men might be lost in the turmoil of their own institutions. Surely this is why kindness as well as intelligence radiates from every one of his photographs. And this is why we not only think well of Dr. Klemperer but also feel strongly toward his memory.

He was a large man in every spiritual dimension. Let future generations produce his equal if they can.

SAUL JARCHO, M.D.
for the
EDITORIAL BOARD



ELI MOSHCOWITZ, M.D.
1879-1964

In Memoriam

ELI MOSCHCOWITZ

1879-1964

On the morning of February 23, 1964, with the strains of his favorite music echoing softly in his room, the life of a beloved friend and colleague quietly slipped away. For over sixty years Eli Moschcowitz was intimately identified with The Mount Sinai Hospital and the loss of one who labored so diligently in its behalf, and who did so much to enhance its reputation, will be irreplaceable.

Despite his growing weakness in his advancing years, he had maintained his keen interest in ministering to his patients to the day before he died. His remarkable zest for living had carried him so successfully through fourscore and four years of life that he was also planning his annual trip to some foreign land. Those who mourn his passing are grateful for the sparkling memories of those years he shared so wholeheartedly with us all.

Eli was born in the tiny village of Giralt, Hungary, in 1879. At the age of two he emigrated with his family to the United States. His older brother, Alexis, whom he revered, unquestionably exerted a most profound influence upon his life. This dynamic surgeon-brother acted *in loco parentis* and guided the youthful Eli's steps toward the medical career in which he found such fulfillment and which he so enriched. He was graduated from the College of Physicians and Surgeons in 1900. He completed a surgical internship at Mount Sinai Hospital in 1903 and, as was customary in those days, then journeyed to Berlin for postgraduate study. There he worked with Ludwig Pick, an eminent pathologist. This training did much to fashion his career as it was in the laboratory that he was able to find verification for the keen observations his great clinical sense afforded him. I do not believe that he ever seriously thought of pursuing surgery as his life's work but he always spoke in glowing terms of his training at the hands of that "giant" surgeon and intellect, Arpad Gerster.

Upon his return to America, he was thus equipped to become pathologist to the Beth Israel Hospital, a position he held for twenty years until the press of practice and his appointment to the visiting staff of Mount Sinai made it impossible for him to continue in this capacity. However, he remained there as Consulting Pathologist.

It was during his tenure at the Beth Israel Hospital that he described the clinical and pathological features of a case of "Acute Febrile Pleomorphic Anemia with Hyaline Thrombosis of Arterial Capillaries, an Hitherto Undescribed Disease." It has since been called Moschcowitz's Disease although at the present time it is often referred to as thrombotic thrombocytopenic purpura. This established him as a keen observer and his communication merited an editorial in the Journal of the American Medical Association.

It followed only naturally that in 1920 he was appointed to the visiting staff of our Hospital and in 1925 became Associate Physician. He was appointed Physician to the Hospital in 1941, a post he filled so ably until retirement in 1944 when he became Consulting Physician.

Dr. Moschowitz was a scholarly chief, teacher and guiding spirit. The house staff was indoctrinated with the finest in medicine. He was always willing to share his creative thinking and to provide opportunities for his staff. He never stooped to clinical showmanship but his erudition and vast knowledge of the literature made him an outstanding diagnostician and his judgments were impeccable.

Eighty-odd publications, some unique, all meritorious, comprised a bibliography published in 1945 in connection with a "Festschrift," marking his retirement from active hospital service. There was no field of medicine his work did not explore. His articles were written with discernment and bore the stamp of indefatigable hard work. "He touched nothing he did not adorn."

It would be presumptuous for me to evaluate or give precedence in importance to the many articles he penned. But there is little question that his work on vascular sclerosis with particular reference to intravascular tension as a biological factor in the causation of blood vessel disease, pointing out as he did venous sclerosis in hypertension of the lesser circulation, will constitute a monument to his logical deductive reasoning, reinforced as it was by meticulous, detailed pathological study of autopsy material.

He published the first Mount Sinai Monograph in 1948, titled *Biology of Disease*, comprising twenty-four chapters, each covering a disease entity seemingly dissimilar but emphasizing that "many diseases are not sharply defined genera but transitions of morbid states from one to another."

He was a pioneer in drawing attention to the influence of the psyche in initiating, influencing and perpetuating disease states. In his article, "Psychosomatic Medicine," he early drew attention to Graves's Disease and ulcerative colitis as prototypic and closed his article expressing the hope that in hospitals "People should be treated and not diseases."

In 1945 Eli became Director of Medicine Emeritus. Yet he remained the busy practitioner and consultant with even broader scientific interests. Each afternoon was spent in the laboratory with his close friends and colleagues, Dr. Otani and the late Dr. Klemperer, searching for the verities and writing just as prolifically as ever. His enthusiasm knew no bounds and his enjoyment of work seemed to add years to his life and put life in his years.

His interest and devotion to the laboratory in no way detracted from his deep concern for human beings and his patients were devoted to him. He was their confidant, teacher and counselor. As he so aptly put it, "Doctors must teach people how to live as well as how not to die." In the lives of his patients, he will be irreplaceable.

His love for The Mount Sinai Hospital was enduring and pervaded every fiber of his being. He entered into every activity that promoted the Hospital's

reputation with verve and gusto. He worked industriously in the modernization of the Jacobi Library and was active in its behalf until his demise.

So much for the factual outline of Eli Moscheowitz's outstanding career. But his medical accomplishments are as nothing compared to the human qualities he shared so graciously with his many friends. His great sense of humor, never employed at the expense of any person, but always benign; his wide fund of knowledge given without showmanship; his pixyness which endeared him to children and whom he, in turn, loved, was genuine and sincere.

He embraced the humanities and the arts in all their variegated forms. His book collections and prints afforded him tremendous enjoyment and he liked nothing better than displaying his collection and autographs to visitors. It was a privilege to have traveled with him for he was a guide par excellence.

It will be difficult to walk the halls of this Hospital without believing that he will appear as of yore, giving us his inimitable evanescent handshake. Eli will long be missed and truly mourned.

PERCY KLINGENSTEIN, M.D.
for the
EDITORIAL BOARD

A Substance Obtained from a Staphylococcus Which Rapidly Enhances Resistance to Infection

I. Observations with Staphylococcal and E. coli Infections

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INTRODUCTION

Resistance to infection is a resultant of many factors. Some of these factors are species-specific but many are shared by a great many animal species. Some resistance factors are effective against a specific infectious agent only, while others play a nonspecific role in the general resistance to a variety of pathogenic organisms. A number of substances which possess no direct antimicrobial power are known to enhance nonspecific resistance to infection. A better understanding of "natural resistance" might be expected to result from the study of these resistance-enhancing substances. Endotoxins have been shown to have resistance-enhancing properties, but they have other properties which include the production of fever, changes in white blood cells and in blood vessels. These "side effects" may interfere with an understanding of some of the basic mechanisms by which endotoxins enhance resistance to infection. Consequently, efforts have been made to chemically modify endotoxins to dissociate their biological effects (1).

This communication is a report of studies made with a substance extracted from a strain of *Staphylococcus aureus*. We have found that this staphylococcal extract (SE) has resistance-enhancing activity similar to that of endotoxins, but it has none of the toxic properties of endotoxins.

In an earlier paper (2) we reported that within twenty hours after receiving SE intra-abdominally, adult and suckling mice were protected against lethal infection with homologous and heterologous strains of staphylococci and a toxigenic strain of *E. coli*. It was found that it made little difference whether the staphylococci or *E. coli* were injected intra-abdominally or intracerebrally, proving that the protective effect elicited by SE was systemic and not local. However, selection of the proper dilution of challenging organisms was critical. If the challenge dose of bacteria was too large, the protective effect was obscured. The protective activity of SE could best be observed if the effect of the highest dilution of organisms which killed more than 50 per cent of the control

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mice was studied. In all experiments SE was made from the Bartlett strain of *Staphylococcus aureus* (2), and in most experiments the animals were challenged with this organism. However, in three experiments other bacteria were used as challenge organisms. These were the "H" and "Giorgio" strains of *Staphylococcus aureus* and a strain of *E. coli* 0111:B4. The results showed that the enhancement of resistance was not limited to the organism from which the SE was obtained. We also showed that the protective effect against staphylococcal challenge was unrelated to the size and age of the mice.

In the experiments to be presented here the work noted above was extended chiefly by using rabbits which were challenged with staphylococci and large numbers of suckling mice which were challenged with *Staphylococcus aureus* or *E. coli*. An additional aim was to investigate the physical, chemical and pharmacological nature of the resistance-enhancing factor in the staphylococcal extract.

MATERIALS AND METHODS

Animals

The *rabbits* were New Zealand albinos and weighed 2 to 3 kilograms each. They were obtained from Rockland Farms.

The *suckling mice* were all of the Swiss CFW strain. They were 2 to 4 days old and each weighed approximately 1 gram. They were kept in groups of 5 to 8 with a mother in a single glass jar. They were obtained from Carworth Farms.

Bacteria

Staphylococci—The "Bartlett" strain, which was obtained from Dr. David Rogers, was used for preparation of the extract and for challenge. This is a coagulase and mannitol positive *Staphylococcus aureus*. It is resistant to penicillin and its bacteriophage type is 80-81.

E. coli—A toxigenic strain, type 0111:B4, was used.

All organisms were maintained on plain agar slants. When used for challenging animals, the bacteria were grown for 4 hours at 37°C in trypticase soy broth and then 0.1 ml was inoculated into 40 ml of the same medium. This culture was incubated for 18 hours and the organisms separated by centrifugation. They were suspended in sterile saline, and the concentration determined by plating of several dilutions on blood agar plates.

Staphylococcal Extract (SE)

Centrifuge tubes containing 40 ml of trypticase soy broth were each inoculated with 0.1 ml of a 4 to 6 hour culture of the "Bartlett" strain of staphylococcus. After 18 hours of incubation at 37°C the culture tubes were centrifuged and the sedimented bacteria discarded. The supernate from each tube was acidified by the addition of 0.5 ml of glacial acetic acid, giving a final

concentration of 1.5M acetic acid. The acidified supernates were then boiled over a hot plate until they were reduced to approximately 1/40 of their original volume. The concentrates were filtered through glass wool and pooled. The filtrate was added dropwise to 7 volumes of 95 per cent ethyl alcohol. The precipitate was collected by centrifugation and dried under a vacuum. At first it was stored in this state at 4°C. However, after it was determined that the resistance-enhancing factor was not destroyed by lyophilization (see text), it was stored in the lyophilized state. It was reconstituted by the addition of distilled water.

Experimental Disease in Suckling Mice

An infection which usually resulted in death between 8 and 24 hours was produced by injecting suckling mice intra-abdominally with carefully determined numbers of *Staphylococcus aureus* or *E. coli*. When staphylococci were used, the inoculum was 0.03 ml of a mixture of equal parts of saline suspension of organisms and 0.5 per cent Triton X-100. Triton X-100 is a substance which is nontoxic in this concentration and produces a mucinlike enhancement of virulence (3). The number of staphylococci uniformly required to kill more than 50 per cent of the mice was 2×10^7 . When *E. coli* were used no Triton X-100 was required. The effective dose of *E. coli* organisms was 3×10^7 , contained in a volume of 0.03 ml. Animals dying before 8 hours were not considered in the evaluation of the experiment. Experiments were terminated at one week.

Experimental Disease in Rabbits

A staphylococcal disease was produced by inoculating rabbits intravenously with 2 ml of a saline suspension containing 2×10^8 staphylococci. This resulted in death within a four-week period of two-thirds of the control animals. Within 24 hours, they usually developed a 2 to 3 degree elevation in temperature which persisted for as long as 10 days, or until death supervened. Most of the animals that died did so within the first week of disease. During their illness, the rabbits ate little and often lost as much as 30 per cent of their weight. Experiments were terminated after four weeks.

Protection Experiments

Animals were given an intra-abdominal injection of either staphylococcal extract or an equal volume of sterile normal saline. Suckling mice were given 0.03 ml and rabbits 20 ml. After a short period, usually 20 hours, an attempt was made to produce either staphylococcal or *E. coli* disease. The results were compared and analyzed statistically by the chi square method.

RESULTS

A. Suckling Mice

Table I summarizes the results of representative experiments with suckling mice in which the bacteria used for challenge were either *Staphylococcus*

aureus or *E. coli*. A significant enhancement of resistance to infection with both of these organisms is demonstrated in the extract-treated sucklings. This result is comparable to that previously shown by us with adult mice (2). Consequently, suckling mice were used in all subsequent mouse protection experiments since larger numbers of these animals could be handled. Ekstedt (4) has recently shown that with staphylococcal infections in adult mice the results may be so variable that groups of at least 15 to 20 animals must be used for reliability.

TABLE 1
Protective Effect of Staphylococcal Extract in Suckling Mice

Intra-abdominal Challenge	Exp.	Preliminary Saline (.03 ml IA*)			Preliminary Crude Extract (.03 ml IA)		
		No. of Mice	Deaths	Survivors	No. of Mice	Deaths	Survivors
2×10^7 Staph. + Triton X-100	1	40	27	13	48	18	30
	2	41	32	9	35	7	28
	3	37	19	18	38	4	34
Total		118	78	40	121	29	92
				40/118 or 34% survivors			
				92/121 or 76% survivors			
				$\chi^2 = 42.89$ $p = <.001$			
3×10^7 <i>E. coli</i>	1	35	27	8	37	13	24
	2	36	18	18	36	4	32
Total		71	45	26	73	17	56
				26/71 or 37% survivors			
				56/73 or 76% survivors			
				$\chi^2 = 19.58$ $p = <0.001$			

* IA—intra-abdominally.

B. Rabbits

In order to learn whether the protective effect was restricted to mice a few experiments were carried out in which adult rabbits were given a preliminary intra-abdominal injection of 20 ml of extract or saline. After 20 hours they were challenged intravenously with staphylococci. At the time the 20 ml of extract seemed to be a convenient amount, but subsequent calculations indicated that on a proportionate weight basis this represented only about $\frac{1}{3}$ the amount given to the mice. There were a total of 21 rabbits in each group. At the end of four weeks there were 7 survivors among the 21 controls, and 12 survivors

among the 21 extract treated rabbits. These numbers are too small to be significant. However, when autopsies were done in 28 consecutive animals, we did gain the impression that the relatively small amount of extract had afforded some protection. Animals dying within the first 24 hours showed no gross pathology. Those dying after that time usually showed multiple abscesses in the kidneys, and less often also in the lungs and liver. In Table II the degree of pathology in the rabbits that died and were autopsied is roughly quantified. The pathology was graded plus 5 if both kidneys, both lungs and the liver showed abscesses. It was plus 4 if lesions were found in only 4 of these organs, plus 3 if lesions were present in only 3, etc. There were 10 deaths among the 14 rabbits in this control group, and out of a possible 50 pluses, there were 34 (68%). There were only 5 deaths among the 14 animals in this extract treated group, and out of a possible 25 pluses, there were only 4 (16%).

C. Concentration and Partial Purification of the Protective Substance

The most fruitful method so far for concentration and partial purification of the protective substance in the staphylococcal extract has been DEAE

TABLE II
Protective Effect of Staphylococcal Extract in Adult Rabbits

Preliminary Treatment	No. of Rabbits	Deaths	Extent of Gross Pathology
Extract	14	5	16% (4/25)*
Saline	14	10	68% (34/50)*

* Number of areas actually involved

Number of possible areas for involvement

—Sephadex chromatography using a stepwise gradient of increasing molarity and decreasing pH. An eluate peak was obtained which gave good enhancement of resistance. The results of three experiments using three different samples of this peak are shown in Table III. As can be seen 0.1 mg of this material was more effective than 1 mg of the original. Indeed this eluate may be even more than 10 times as effective, but we have not yet had an opportunity to determine the limits of its effectiveness.

It should be noted also that the crude extract sensitized red blood cells so that they were agglutinated by sera containing antistaphylococcal antibodies (5). The purified material did not have this property.

D. Physical Properties of the Protective Substance

The extract containing the protective substance is light brown in color. It is very soluble in water and saline. It is insoluble in alcohol, ether, acetone and phenol. Because of the way in which it is prepared—boiling at acid pH—it was anticipated that it would be quite stable. This proved to be the case. It withstood storage in the cold for one week. Treatment of the extract with ammonium sulfate so that there was 75 per cent saturation gave a precipitate

which contained most of the resistance-enhancing activity. This activity was not lost by dialysis or by lyophilization. The extract was decomposed by heating at 193°C.

E. Preliminary Chemical Characterization

Dr. Nathan Epstein and Mr. George Mayers in our laboratory are investigating the chemical nature of the active fraction they obtained for us by chromatography. Their work to date suggests that the active material is a polysaccharide or a mucopolysaccharide. It has a pentose, a hexosamine and a nitrogen-containing group. The pentose on paper chromatography migrates as a ribitol. This suggests that the substance may be related to the teichoic acids which have recently been reported to be present in the cell wall of *Staphylococcus aureus* (6).

TABLE III
Results of Testing Extract Purified by Chromatography in Suckling Mice*

Challenge	Exp.	Preliminary Saline (.03 ml 1A)			Preliminary Chromato- graphic Peak (approx. 0.1 mg 1A)			Preliminary Crude Extract (approx. 1.0 mg 1A)		
		No. of mice	Deaths	Surviv- ors	No. of mice	Deaths	Surviv- ors	No. of mice	Deaths	Surviv- ors
3×10^7 E. coli Intra- abdominally	1	30	24	6	28	7	21	24	8	16
	2	26	23	3	26	8	18	26	19	7
	3	25	20	5	27	0	27	25	9	16
Total		81	67	14	81	15	66	75	36	39
		14/81 or 17% survivors			66/81 or 81% survivors			39/75 or 52% survivors		
					$\chi^2 = 66.77$ $p = < .001$			$\chi^2 = 20.92$ $p = < .001$		

* Chromatography done on DEAE-Sephadex.

F. Pharmacological Studies

A large number of toxicity studies were done with rabbits, guinea pigs, and suckling and adult mice. A mortality rate of one per cent was encountered when suckling mice were injected intra-abdominally with either 6 mg of crude extract or with an equal volume of normal saline. In guinea pigs repeated weekly doses of extract did not result in anaphylaxis. When the extract was given to adult rabbits intravenously, neither the leukopenic nor pyrogenic effects which have been described after endotoxins were observed. No toxic effects were noted in rabbits when doses as large as one gram were given intravenously. Repeated intradermal injections in rabbits and in mice produced no local reactions. Attempts to produce a Schwartzman phenomenon or enhanced reaction to intradermal epinephrine also gave consistently negative results. The

addition of extract to nutrient fluid in 10 per cent concentration produced no visible effect on Hela, monkey or rabbit kidney cells in monolayer tissue culture.

Even 100 mg of extract had no unfavorable effect on the growth on staphylococci and *E. coli* *in vitro*. In Table IV the results are summarized of a test in which the *in vitro* effect of the extract is compared with that of chloramphenicol. For this test a series of test tubes containing 1 ml of trypticase soy broth were set up. Various amounts of extract or chloramphenicol in 0.1 ml volume were added to each tube. Tenfold dilutions were made of 6 hour bacterial cultures, and 0.1 ml of appropriate dilutions were added to each of the tubes containing the material to be tested. After incubation for one hour at 37°C, 0.2 ml from each tube were spread on well-dried trypticase soy agar plates. At the end of an 18 hour period of incubation at 37°C the number of colonies on each plate was counted and compared.

When given to suckling mice, a dose of extract of at least 0.6 mg of extract per animal was required to bring about enhanced resistance. Once the

TABLE IV
In Vitro Effect of Extract (SE) and Chloramphenicol on Growth of Bacteria

Bacteria	Number of Colonies on Each Plate						
	SE				Chloramphenicol		Broth
	10 mg	1 mg	0.1 mg	0.05 mg	50 mg	5 mg	—
<i>S. aureus</i>	91	96	96	112	0	0	94
<i>E. coli</i>	225	299	211	219	2	76	253

process was "triggered," there did not seem to be a proportionate increase in effectiveness with increasing amounts of extract. This can be seen in the representative experiment shown in Table V. Despite the fact that there was a tenfold difference in amount of extract given to the two groups of mice which showed protection, there was no significant difference in the degree of protection. Other experiments support the belief that 0.6 mg of the lyophilized crude extract is close to the minimal dose needed to bring about protection in the suckling mice.

The giving of repeated daily injections of extract also failed to bring about an increase in effectiveness once the enhanced resistance was "triggered." This is shown in the experiment summarized in Table VI. (It is of interest that there were no untoward effects from the multiple injections of extract.)

Perhaps the most significant observation regarding the resistance-enhancing property of the extract is that its effectiveness is dependent upon time. A few hours are required after the extract is given to demonstrate the effect and the effect persists for only a few days. This is shown in the experiments summarized in Figure 1. In these experiments, all treated sucklings received 6 mg of the crude extract. There was a saline treated control group for each time interval.

E. coli was the challenge organism. For each time interval the number of survivors among the extract-treated mice was compared with the number of survivors in the control group. The chi square values were determined and plotted on the vertical axis. The time interval between treatment and chal-

TABLE V

*Effect of Amount of Lyophilized Crude Extract on Protective Effect in Suckling Mice**

Saline			Extract								
No. of Mice	Deaths	Survivors	(6 mg/animal)			(0.6 mg/animal)			(0.1 mg/animal)		
			No. of Mice	Deaths	Survivors	No. of Mice	Deaths	Survivors	No. of Mice	Deaths	Survivors
73	48	25	73	21	52	80	31	49	72	48	24
25/73 or 34% survivors			52/73 or 71% survivors $\chi^2 = 20.0314$ $p = <.001$			49/80 or 61% survivors $\chi^2 = 11.144$ $p = <.001$			24/72 or 33% survivors		

* Preliminary injection—0.03 ml intra-abdominally. Challenge— 3×10^7 *E. coli* in 0.03 ml intra-abdominally.

TABLE VI

*Effect of Multiple Preliminary Doses of Extract on Protective Effect**

3 Doses						2 Doses						1 Dose					
Saline			Extract†			Saline			Extract			Saline			Extract		
No. of Mice	Deaths	Survivors	No. of Mice	Deaths	Survivors	No. of Mice	Deaths	Survivors	No. of Mice	Deaths	Survivors	No. of Mice	Deaths	Survivors	No. of Mice	Deaths	Survivors
28	22	6	22	6	16	29	22	7	28	3	25	30	23	7	25	5	20
6/28 or 22% survivors			16/22 or 73% survivors $\chi^2 = 13.1572$ $p = <.001$			7/29 or 24% survivors			25/28 or 89% survivors $\chi^2 = 25.57$ $p = <.001$			7/30 or 23% survivors			20/25 or 80% survivors $\chi^2 = 17.52$ $p = <.001$		

* All injections were given intra-abdominally in volume of 0.03 ml per suckling mouse. 24 hr. intervals between doses—except last dose which was given 20 hrs. before challenge. Challenge: 3×10^7 *E. coli*.

† Extract crude lyophilized. Dose—6 mg/animal.

lenge was plotted on the horizontal axis. Figure 1 shows that it takes about 6 hours before a high level of protection is attained. This protection continues for 42 hours. Then, there is a sharp drop and at 48 hours no protection is demonstrable.

The duration of resistance may vary with different animals and challenging bacteria. In one earlier experiment adult mice, which had been given approximately the same amount of extract on a body-weight basis as the above sucklings, were challenged at appropriate times with staphylococci. Significant protection could be demonstrated for at least 72 hours.

DISCUSSION

The use in the laboratory of bacterial products which within 24 hours modify the course of infections goes back at least to the last century (7).

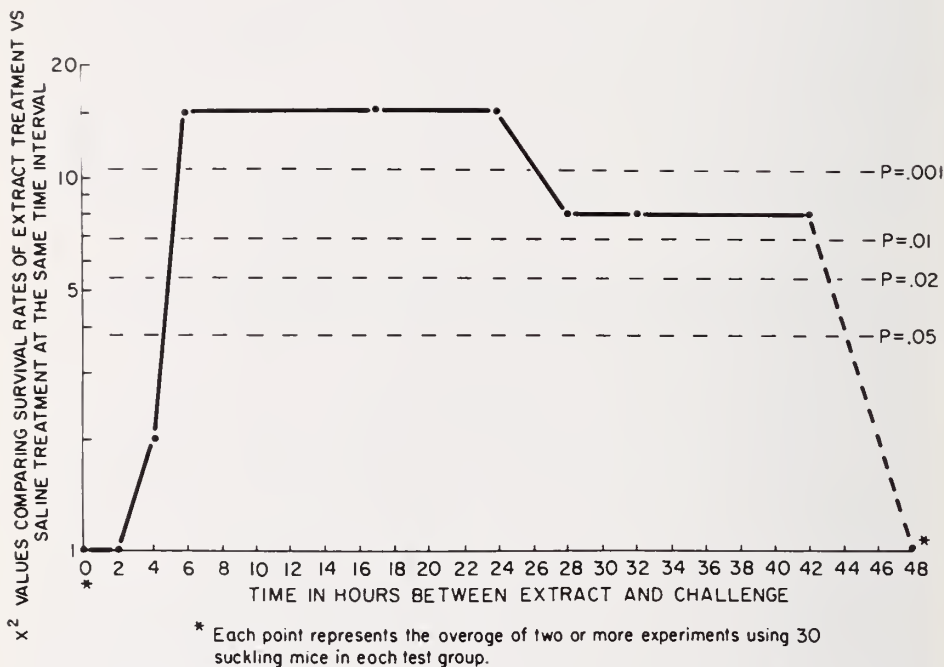


FIG. 1. The effect of the time interval between injection of extract and challenge injection of bacteria.

However, until about 10 years ago there was relatively little interest in such substances, unless they were antimicrobials. Recently there has been a renewed interest in endotoxins and other bacterial substances which do not possess direct antimicrobial activity (8). One of the many experimental reactions elicited by endotoxins is that of rapidly enhancing nonspecific resistance to infection.

The staphylococcal extract described in this communication is not an endotoxin, but it does rapidly induce protection which is nonspecific. It does this not only when given to adult mice, but also when given to sucklings which have had very little opportunity for previous exposure to the bacteria used for challenge. We have shown that the extract protects suckling mice equally well against two different bacteria—staphylococci, which are destroyed within

phagocytes, and *E. coli*, which are destroyed by humoral factors alone. The effect of the extract probably is not limited to these two infectious agents. We have carried out a few experiments which suggest that the extract may afford some protection to suckling mice against *H. simplex* virus (9). In addition, it has recently been reported by Schaffer and co-workers (10) that preliminary treatment of suckling mice with a staphylococcal extract resulted in an increased degree of resistance to infection with Coxsackie B1 virus.

The protection which seemed to be afforded to the treated rabbits suggests that the extract may be effective in a variety of animal species. We have not yet had an opportunity to test this possibility in other species.

The lack of toxicity of our extract is remarkable. It can be given in large and repeated doses to mice and rabbits without producing signs of illness. This is in contrast to the results reported by Sultzzer and Freedman (11) with two staphylococcal extracts which contained lipopolysaccharides. Pretreatment with their material did protect mice against subsequent lethal challenge with *E. coli*. However, their staphylococcal extracts produced biphasic fever and a leukopenic response in rabbits. Our substance which was also derived from a staphylococcus did not behave like an endotoxin in rabbits. Neither did it damage guinea pig monocytes as did *E. coli* endotoxin in tests done for us by Dr. Mehdi Shayagani at the Rutgers University Institute of Microbiology.

The extract is nonantigenic for mice, rabbits, and guinea pigs. In our earlier report (2) it was noted that pools of serum obtained from mice two weeks after injection did not contain staphylococcal antibodies which could be detected by bacterial agglutination, hemagglutination or latex fixation. As a part of the present study, rabbits were given large doses of extract intra-abdominally and their sera tested after 24 hours and again after two and four weeks for the presence of staphylococcal agglutinins and hemagglutinins. Although it is well known that commercially raised rabbits often have naturally-acquired antibodies (12) no rise in titer could be demonstrated.

The protection elicited by staphylococcal extract is limited in degree and time. If too large a challenge dose is given, the protective effect cannot be demonstrated. It requires several hours to appear, and it persists for only a few days. Yet the variety of infectious agents against which the extract elicits enhanced resistance, and the fact that it does this in newly born as well as older animals suggests that it may stimulate an important mechanism of "natural immunity." If we understood the mode of action of the extract, we might be in a position to prepare a "strategically different way to control infectious disease" (13). The lack of toxicity and antigenicity of this substance suggests that it may have wide application in experiments designed to study in detail the complex factors which make up "innate resistance" to infection.

The manner in which the extract elicits protection is not clear. It has no *in vitro* inhibitory effect on the growth of bacteria. When the extract is given to mice there is a definite period of time which must elapse before the animals show increased resistance. During this time some mechanism is put into action which very quickly brings about a maximum effect. The effect of the extract

is not increased either by larger doses or by repeated doses. It has been suggested by Whitby *et al.* (14) that endotoxins enhance protection by bringing about a rapid release of bactericidal antibody. If this were true of our extract it would have to occur within six hours in newly born mice. This is a very short period within which to induce primary antibody production. Braun *et al.* (15) showed that DNA breakdown products may stimulate antibody synthesis, and that if they are given with a sub-effective dose of endotoxin there is a significant increase in the resistance of the mice. However, when we gave a mixture of subminimal effective doses of *Salmonella typhosa* endotoxin (Difeo) (0.001 μ g) and our extract (0.1 and 0.2 mg) to sucklings and then challenged them with *E. coli*, no protection was demonstrated. (In preliminary titrations 0.003 μ g of the endotoxin and 0.6 mg of the extract were effective.) Thus far we have failed to find any consistent change in the peripheral white blood cell count of adult mice or rabbits after they had been given a dose of extract sufficient to elicit protection. We have not yet investigated what effect the extract may have on cells of the reticulo-endothelial system. The studies of Rowley (16) and others (17) with endotoxins suggest that such studies may be fruitful.

SUMMARY

1. Acidification and boiling of the supernatant of an 18 hour culture of an epidemic strain of a type 80-81 staphylococcus yielded a substance which was precipitable in ethanol and soluble in water. Intra-abdominal injection of an aqueous solution of this substance significantly increased the ability of suckling and adult mice to withstand staphylococcal and *E. coli* infections which were lethal to more than 50 per cent of control animals. The substance also afforded some protection to rabbits challenged by intravenous injection of staphylococci. The protection given these animals was of a general systemic nature.

2. The protective substance was not toxic and not antigenic. It withstood lyophilization and could be concentrated and partially purified by DEAE-Sephadex column chromatography. Preliminary chemical analysis indicates that it has pentose, hexosamine and a nitrogen-containing group.

3. The protective staphylococcal extract had no *in vitro* inhibitory effect on the growth of staphylococci or *E. coli*. However, when it was given to animals in sufficient amounts, it appeared to "trigger" a protective mechanism. There was no proportionate increase in activity with increased dosage. Neither was there any increased activity after repeated daily injections. Time was required before enhanced resistance could be demonstrated and it persisted for only a limited period.

4. Some of the possible mechanisms by which the protective substance may bring about enhanced resistance and their implications are discussed.

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Cardiodynamics of Pericardial Disease*

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Three main syndromes have been produced by diseases of the pericardium: that dominated by precordial pain due to acute inflammation of the pericardium; that due to acute pericardial effusion, with or without manifestations of venous congestion; third, a chronic constrictive process which is associated with a small or moderately enlarged cardiac silhouette and which interferes with ventricular filling. More recently, a fourth syndrome has been delineated, that due to chronic, massive pericardial effusion of several years' duration. Important alterations in cardiovascular dynamics may be produced by diseases of the pericardium.

FUNCTION OF NORMAL PERICARDIUM

Normally, there are about 20 to 50 cc of fluid in the potential pericardial space. Major functions of the pericardium include chemical and fluid exchange and a mechanical influence. In the dog, bidirectional shifts of several electrolytes have been demonstrated by isotope studies (1).

The mechanical functions of the pericardium are more important for clinical purposes. Various studies have suggested that at least 80 to 100 cc of fluid may accumulate within the pericardium without producing cardiac compression (2). This is greater than the usual cardiac stroke volume, which is 60 to 80 cc, and this permits moderate cardiac dilatation. In addition, the elastic fibers allow stretching to occur if given enough time. Figure 1 shows a pressure-volume curve of the pericardial sac compared to the curves of the right and left ventricles. There is initially only a slight rise of pressure with substantial increases in volume. The pressure rise then becomes increasingly large with further small volume increments. Stretching of the pericardial fibers has been further demonstrated by the observation that increments of intrapericardial saline must be added progressively to maintain elevations of venous pressure (3).

The function of the pericardium may also be studied by removing it experimentally. Clinically, congenital defect of the pericardium may give no symptoms. However, adjacent infection of pulmonary tissue may extend to the heart and there may be cardiac dilatation with prominence of the atria, an increased transverse diameter and a globular shadow with rounding of the apex. The heart's fluid capacity may be increased.

Interesting experimental observations have been made by Berglund on the role of the pericardium in the regulation of cardiovascular hemodynamics

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(4). When the left ventricle is stressed by aortic constriction, it dilates and right ventricular expansion may be limited by the pericardium. Therefore, pulmonary blood volume may be lower than if the pericardium were absent.

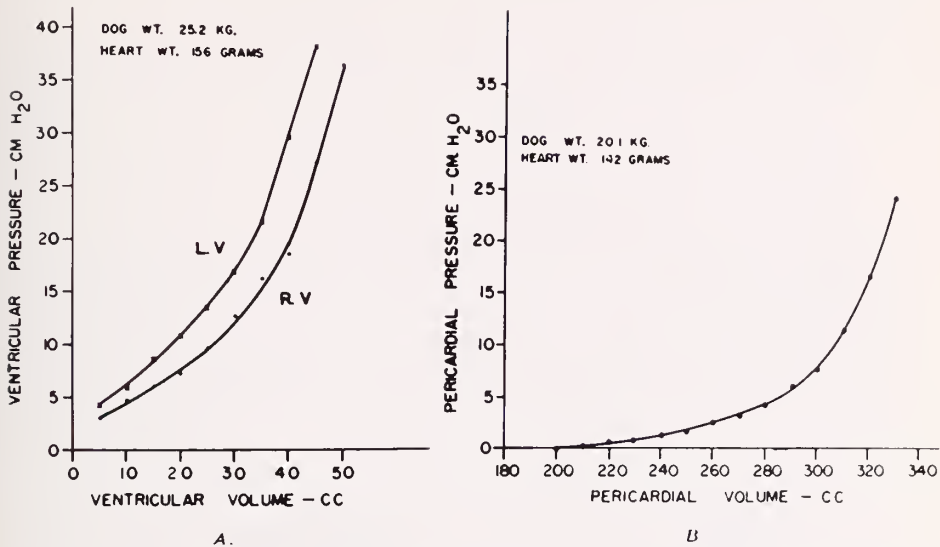


FIG. 1. Pressure-volume curves of the pericardial sac compared to those of the right and left ventricles. It can be seen that the pericardial sac can contain considerable amounts of fluid with only a slight rise in pressure. With further small volume increments, the intrapericardial pressure rises abruptly. (From Isaacs, J. P., *et al.*: *Am. Heart J.*, 48: 66, 1954. Reprinted by permission of author and C. V. Mosby Co., Inc.)

FIG. 2. Pulmonary wedge pressure in dogs following left ventricular stress produced by aortic constriction before and after pericardiectomy. With the pericardium removed, there is a more marked elevation of pulmonary "capillary" or left atrial pressure. (From Berglund, E., *et al.*: *Circulation Res.*, 3: 133, 1955. Reprinted by permission of author and American Heart Association, Inc.)

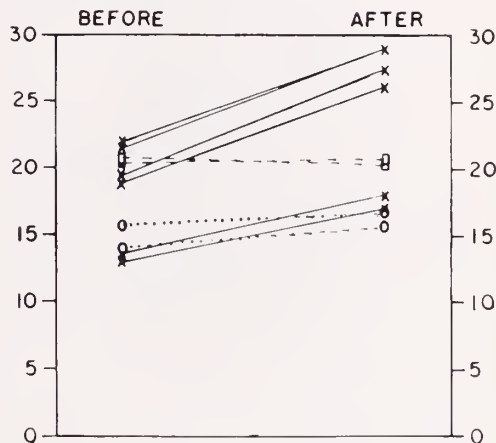


Figure 2 shows that the pericardium limits the elevation of pulmonary "capillary" (and therefore left atrial) pressure when the left ventricle is stressed. There is also some evidence that pericardiectomy may alter the "Starling curve" (Fig. 3). As the venous pressure is raised by infusion, deterioration

of the Starling curve may occur sooner in the pericardiectomized animal than in one in which the pericardium is normal. However, when peripheral resistance is elevated, a heart without pericardium sustains a satisfactory output longer than a heart with intact pericardium (Fig. 3).

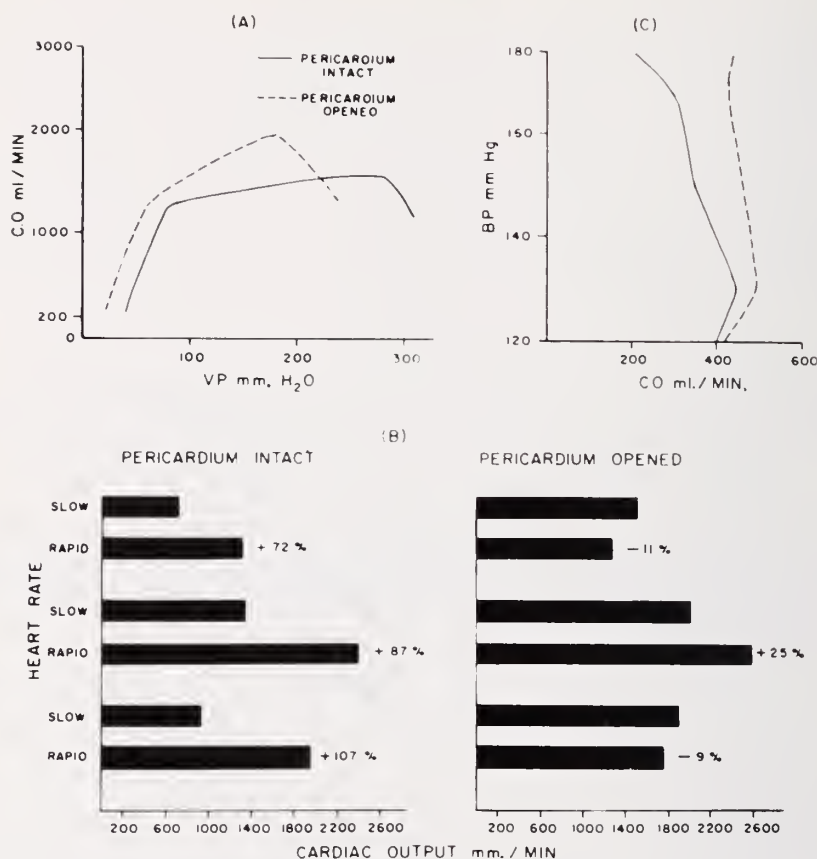


FIG. 3A. Cardiac performance is altered by pericardiectomy. Cardiac decompensation occurs at a lower venous pressure than with the pericardium intact.

FIG. 3B. When the pericardium is opened, there is little increase in cardiac output with tachycardia, in contrast to the animal with an intact pericardium.

FIG. 3C. When the arterial pressure is elevated, there is a more precipitous fall in cardiac output when the pericardium is intact than when it is open. (Adapted from Kuno (5). In Spodick, D. H.: *Acute Pericarditis*. New York: Grune and Stratton, 1959. Reprinted by permission of author and publisher.)

Cardiac output response to rate fluctuations is aided by the pericardium. The normal increase in cardiac output with tachycardia is not obtained in the animal with an open pericardium (5) (Fig. 3). Although there may be little clinical effect in the pericardiectomized human subject, the diastolic volume is large at rest and probably greater than normal during exercise. While a normal heart may dilate after vagal stimulation, such stimulation may produce even more dilatation after pericardiectomy (6).

From these considerations, it appears that the normal pericardium limits excessive cardiac dilatation and in response to inflow loads maintains an appropriate "Starling curve." In addition, it promotes adequate cardiac output response to rate changes and limits undue displacement of the heart by reason of its external attachments. However, when heart failure is produced by increased peripheral vascular resistance an intact pericardium may be a disadvantage and may be associated with a more rapid decline in cardiac output.

PERICARDIAL EFFUSION

A. Hemodynamic Effects

Acute pericarditis may alter cardiac dynamics very little in its "dry" state, but if pericardial effusion occurs, there may be important dynamic changes.

Both clinical observations and experimental studies have provided information as to the physiologic alterations which occur during pericardial effusion. The hemodynamic effects of effusion are closely related to the speed of accumulation of the fluid. The rapid accumulation of 150 to 200 cc may produce acute cardiac tamponade whereas the slow accumulation of a liter or more may be well tolerated and in some cases as much as 4 liters may not interfere too greatly with cardiac function. Fluid generally accumulates inferiorly, anteriorly and laterally, particularly on the left. Little fluid accumulates directly behind the heart because of firm attachments but there may be posterolateral protrusions of pericardial fluid.

When intrapericardial pressure is increased, diastolic filling of the ventricles is impeded, resulting in a rise in ventricular pressure and a diminution in cardiac output. Figure 4 shows the effects of intrapericardial saline injected into a dog. At a critical level of intrapericardial pressure, there is a precipitous fall in arterial pressure accompanied by a rise in left and right atrial pressures and eventually a flowless system. Although the atrial pressure is elevated, the effective filling pressure (that is, the atrial minus the intrapericardial pressure) is diminished and the stroke work of both ventricles declines parallel with these effective filling pressures. In addition, there are other factors which interfere with cardiac function. Because the filling ends early and the intraventricular pressure rises abruptly, the A-V valves may close prematurely. This may be associated with short fiber length and may further diminish stroke volume. Distinct from the aortic pressure fall, which diminishes coronary perfusion, there are other alterations which also interfere with coronary flow. These are probably due to compression of the coronaries. Possibly because of this, both right and left ventricular function is impaired, as measured by increments of stroke work with increases of filling pressure. The fact that this functional impairment in pericardial tamponade can be rectified by a vasopressor agent suggests that the improvement may be related to increasing an inadequate coronary perfusion (7).

In addition to the direct effects of cardiac compression, indirect effects

may occur. As venous pressure is increased, there may be fluid and sodium retention which lead to edema even before cardiac output and glomerular filtration rate are altered (8). Diminution in cardiac output and renal arteriolar constriction may occur later and further accentuate the sodium retention, although the precise sequence of events is somewhat controversial. Various compensatory mechanisms may affect the physiological changes in pericardial effusion. One of the first of these is tachycardia probably owing to activation

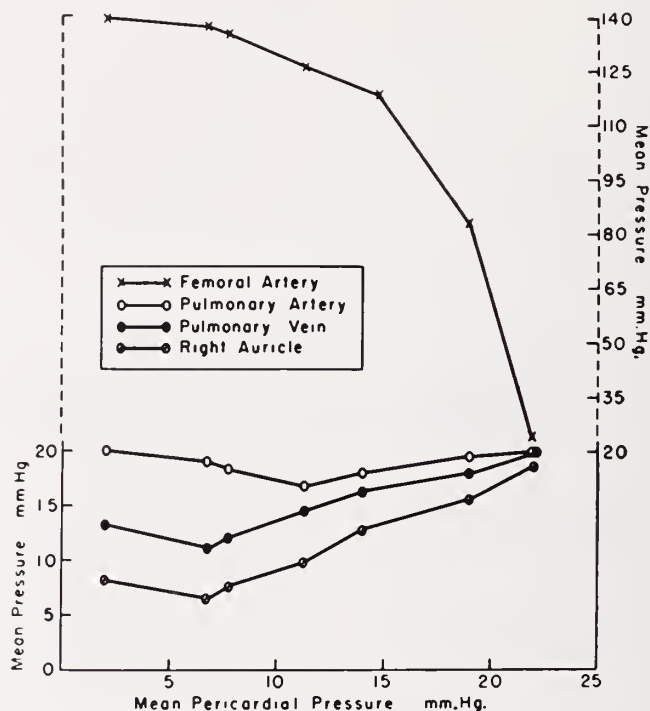


FIG. 4. The effects of intrapericardial saline injected into a dog. At a certain critical level of intrapericardial pressure, there is a precipitous fall in arterial pressure, a rise in atrial pressures and eventually equal arterial and atrial pressures and a "flowless" system. (From Metcalfe, J. P., *et al.*: *Circulation*, 5: 518, 1952. Reprinted by permission of American Heart Assn., Inc.)

of the Bainbridge reflex resulting from right atrial and great vein distention. This maintains total cardiac output despite the fall in stroke volume, but if compression continues this mechanism is insufficient to maintain adequate cardiac output. Because of the fall in cardiac output, reactive vasoconstriction may occur as a compensatory mechanism, and therefore arterial pressure may be well maintained until the final stages of "compensation." During the compensated phase, the cardiovascular adjustments are delicately balanced and sudden increases in cardiac load, such as in exercise, may cause rapid decompensation.

B. *Clinical Manifestations*

The important clinical manifestations of pericardial effusion are directly related to the hemodynamic alterations produced. Symptoms include precordial oppressive pain which may be due to stretching of the pericardium. Various positions of relief are common but many patients do not adopt them. These include sitting up and leaning forward as well as spreading out on hands and knees, the so-called "signe de la prière Mahométane." Dyspnea and orthopnea may appear due to displacement and compression of the lung parenchyma or atelectasis. There may be encroachment on the tracheo-bronchial tree producing cough and an element of airway obstruction. In massive effusions, there may be pressure on the esophagus, with dysphagia, and on the recurrent laryngeal nerve, producing hoarseness. In addition, there may be impingement on the phrenic nerve with resultant hiccough, and nausea and abdominal pain due to a congested liver.

Clinical signs of pericardial effusion include neck vein engorgement and, in advanced compression, precordial venous distention and a precordial bulge. The pulse pressure may be diminished and the pulse rapid. There may be edema and ascites. Two other characteristic signs which should be looked for include "pulsus paradoxus" and inspiratory distention of the neck veins. Normally, inspiration produces a more negative intrapleural pressure and a more positive intra-abdominal pressure, both of which serve to increase right atrial filling. Inspiratory distention of the neck veins occurs because right atrial filling is impeded despite the respiratory increase in venous return. "Pulsus paradoxus" is a misnomer, because it is an exaggeration of a normal response. Normally, despite the increase in venous return with inspiration and hence, right ventricular output, the capacity of the pulmonary vascular bed increases relatively more and there is a resultant fall in left ventricular stroke output with a fall in pulse volume and systolic pressure of about 5 mm Hg. In pericardial effusion, inspiratory right ventricular stroke volume is less than normally increased by an increased venous return because of impaired ventricular filling but the capacity of the pulmonary vascular bed increases on inspiration as it does normally. In addition, the inspiratory improvement in right ventricular filling which does occur results in some expansion of the intra-pericardial contents, causing more left ventricular compression. Both of these result in depression in left ventricular stroke volume and hence in greater than normal fall in systolic pressure on inspiration. Studies of simultaneous pulmonary venous and left atrial pressure during experimental cardiac tamponade have shown a reversal of the normal gradient during inspiration. Under these circumstances there may be reversal of the normal flow in the pulmonary veins (9). Dock has recently emphasized, in addition, that there may be inspiratory traction on the diaphragm, altering the cardiac silhouette sufficiently to cause diminution in left ventricular output and fall in aortic pressure during this phase (10).

A general increase in cardiac dullness may be noted on recumbency, par-

ticularly in the second and third left intercostal spaces. This area may be diminished when the patient assumes a sitting position.

Because of the effusion and possibly early closure of the A-V cusps, the first heart sound may be diminished as may the second sound. An early diastolic third heart sound may appear, due to interference with ventricular filling.

A frequently mentioned finding is the Ewart sign or more correctly, the Bamberger-Pins-Ewart sign. This is an area of dullness and bronchial breathing at the left lung base below the ninth rib. At times this may be noted on the right as well. Angiocardiographic observations by Steinberg have shown that Ewart's sign usually results from compression of the lung, first by a retrodisplaced heart and later by posterior bulging of the lateral portions of the pericardium (11).

Electrocardiographically, in addition to low voltage, more specific find-

TABLE I
Causes of Acute Cardiac Tamponade

Acute pericarditis
Hemopericardium
Following myocardial infarction
Aortic rupture
Lentic or dissecting aneurysm
Coarctation with rupture above ao. valve
Marfan's
Trauma
Neoplasm
Chylopericardium (trauma, neoplasm)

ings have been noted in pericardial effusion. One of these is total electrical alternans. This involves P-waves as well as the QRS complex and is seen with large pericardial effusions. These findings suggest changes in the heart's anatomical position.

Cardiac tamponade results from an acute accentuation of all the factors previously delineated. It can be caused by a variety of conditions as outlined in Table I. Tamponade results from inadequate compensatory responses and is associated with a rising ventricular diastolic pressure and a falling cardiac output. Venous pressure at this point is usually about 150 mm H₂O but cannot adequately maintain right heart filling because of the increasing intrapericardial pressure. It should be realized that a fairly stable cardiodynamic situation may result in tamponade when an additional, relatively small amount of hemorrhage or exudate is added to an existing effusion. Pre-existing pericardial thickening may cause cardiac tamponade when a relatively small effusion is added.

Clinically, the patient may appear to be in shock, with cyanosis, rapid breathing and, sometimes, syncope. The neck veins may show pulsations or inspiratory distention on sitting up. The retinal veins are engorged. The

Beck triad, of a quiet heart, increased venous pressure and diminished arterial pressure may be noted, but is nonspecific.

The syndrome of chronic, massive pericardial effusion has been emphasized relatively recently. This may be caused by a variety of conditions, as outlined in Table II, and may last for many years with or without signs of cardiac compression. It is felt that some of those of "unknown" etiology may represent extensions of an acute idiopathic pericarditis. A few cases characterized by fluid containing cholesterol have been recognized. Although this may be associated with myxedema, some of these patients have been euthyroid. Experimentally, Ehrenhaft (12) has produced chronic pericarditis with effusion by inserting cholesterol suspension into the pericardium of dogs.

C. Differential Diagnosis

A major difficulty is differentiating pericardial effusion from the x-ray shadow produced by enlarged, decompensated hearts resulting from a variety

TABLE II
Causes of Chronic Massive Pericardial Effusion

Unknown etiology
Cardiac and pericardial neoplasms
TB; mycotic diseases
Myxedema
"Cholesterol" pericarditis
Thoracic trauma
"Collagen" disease
Chylopericardium
Post-irradiation

of causes. Pulsus paradoxus is not specific as it may be produced by conditions with exaggerated respiratory maneuvers, such as tracheobronchial obstruction, emphysema and, occasionally, congestive heart failure without these. Inspiratory distention of the neck veins is a more specific sign of cardiac compression, but is not always present. Therefore, usually great reliance is placed on x-ray findings. In the plain film, it may not be possible to differentiate heart from pericardium in the presence of an enlarged cardiac silhouette, although clear lungs are more often a characteristic of pericardial effusion. Serial films, which show rapid enlargement of the cardiac silhouette may be helpful. The pear-shaped shadow, alteration of the silhouette on tilting, diminished pulsations and lack of change in the silhouette with Valsalva or Muller maneuvers all may occur in pericardial effusion but may also occur occasionally with large dilated hearts without pericardial fluid surrounding them. Cardiac catheterization shows a similar high end diastolic ventricular pressure in both congestive heart failure and pericardial compression. An auscultatory differential point has been emphasized by Harvey (13). Normally, when the patient lies on his abdomen and the stethoscope is placed on the anterior chest, the heart sounds will increase in in-

tensity, probably because the heart is thrown closer to the anterior chest. If fluid is present, it collects anteriorly and the sounds will be diminished in this position.

The most reliable techniques of differential diagnosis are those of angiocardiology, as demonstrated in Figure 5. Normally, the right ventricular

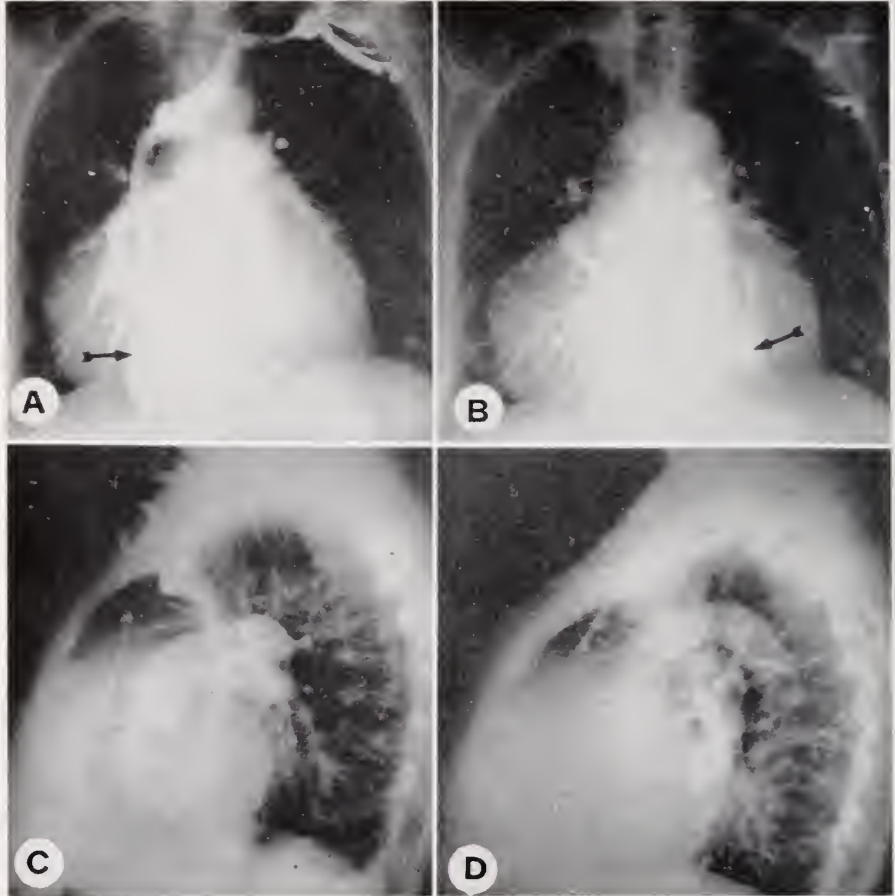


FIG. 5. Right angiocardigrams in a patient with a large pericardial effusion. The arrows indicate the wide space between the border of the heart silhouette and the actual cardiac chamber, filled with dye. (From Steinberg, I., *et al.*: *Am. J. Roentgenol.*, 79: 321, 1958. Reprinted by permission of author and Chas. C Thomas Co., Springfield, Ill.)

wall is 1 to 3 mm thick. In this patient, there is a wide space between the border of the heart silhouette and the actual cardiac chamber. Similar results have been obtained by Durant after the injection of 50 cc of CO₂ which is absorbed rapidly in about 20 minutes and is nontoxic (14). A nonmanipulative procedure has been advocated by Wagner (15). This consists of the injection of radioactive material intravenously and external chest scanning. The size of the cardiac chamber can be delineated. Another technique is that

of Mellins in which kymograms are performed together with a barium swallow in the lateral view (16). In the presence of a large shadow due entirely to the heart chambers, diminished pulsations are noted anteriorly and posteriorly. In pericardial effusion, since the fluid accumulates anteriorly and not posteriorly, the barium will show normal pulsations whereas the kymogram of the anterior border will have diminished pulsations.

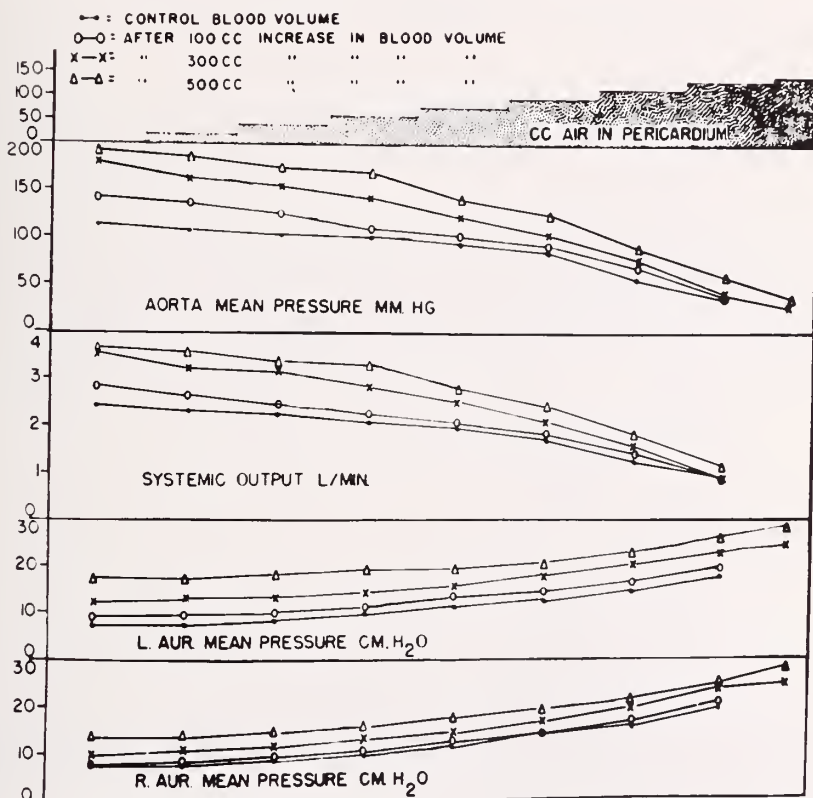


FIG. 6. The effect of an increase in blood volume on the hemodynamic alterations in cardiac tamponade. There is an elevation of arterial pressure and cardiac output when the blood volume is increased during the initial stages of cardiac tamponade. In severe tamponade, blood volume increase produces no improvement. (From Isaacs, J. P., *et al.*: *Am. Heart J.*, 48: 66, 1954. Reprinted by permission of author and C. V. Mosby Co., Inc.)

D. Treatment

While discussion of the treatment of pericardial effusion is beyond the scope of this paper, two points may be briefly mentioned: one is that in performing pericardial aspiration, it should be borne in mind that the fluid accumulates anteriorly and laterally, and not posteriorly. The other is that vasopressors are indicated if the arterial pressure is low, for reasons previously mentioned. Figure 6 shows the effect of increasing blood volume with varying degrees of tamponade. In mild tamponade, increasing the blood volume

elevates arterial pressure and cardiac output significantly, but in severe tamponade there is no significant improvement with increased blood volume. Therefore, blood or plasma expanders may be beneficial if the tamponade is not too severe.

CONSTRICTIVE PERICARDITIS

In chronic constrictive pericarditis, the clinical picture is dominated by prominent venous distention and ascites, out of proportion to any other manifestation of edema. In Figure 7 it can be seen that the rise in portal

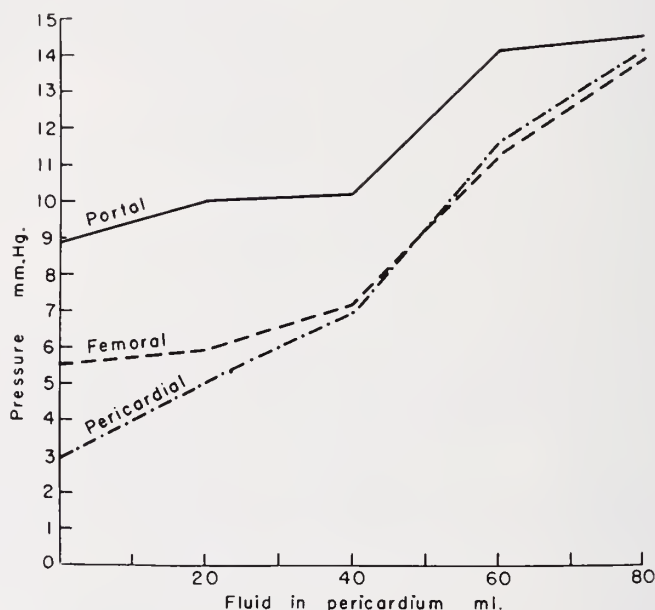


FIG. 7. Alterations in portal and femoral venous pressures during experimental cardiac tamponade. The rise in portal venous pressure is greater than the elevation in femoral venous pressure until the end stages of tamponade. (From Evans, J. M., *et al.*: *Am. Heart J.*, 39: 18, 1950. Reprinted by permission of author and C. V. Mosby Co., Inc.)

venous pressure is greater during tamponade than the elevation in systemic venous pressure until the limits of tamponade are reached which may account for the predominant ascites. This may be due to the fact that fluid collects along the diaphragmatic surface and may give early interference with hepatic and inferior caval inflow.

A second clinical feature of constrictive pericarditis is the frequency of atrial fibrillation, or, in non-fibrillators, of a notched P-wave with the second peak higher than the first. This is probably due to atrial distention secondary to interference with its emptying. A third characteristic is a fairly common third heart sound and closely related to it, a characteristic though non-specific pressure pulse pattern in the right ventricle, the so-called "diastolic dip" (Fig. 8). Actually, this is a misnomer as the low diastolic pressure is normal. What is abnormal is the rapid rise in pressure towards the end of

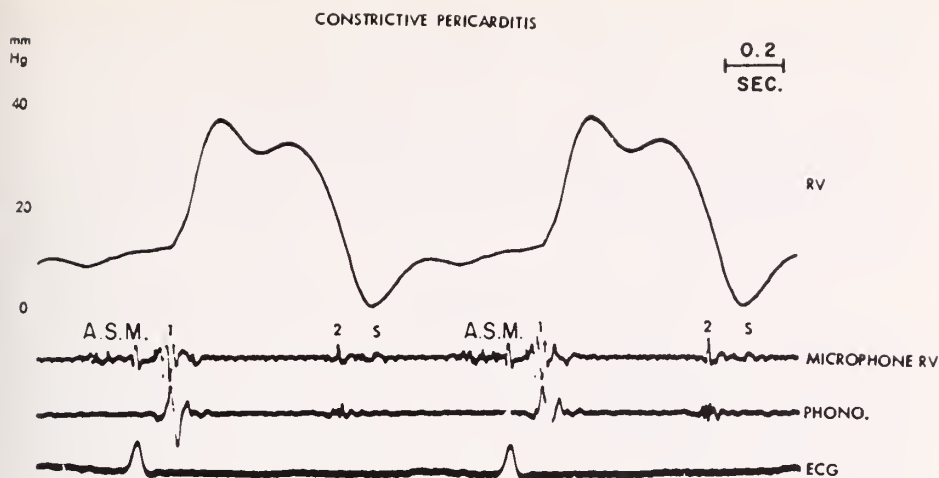


FIG. 8. Right ventricular pressure and right ventricular phonocardiogram in a patient with constrictive pericarditis. The diastolic "dip" consists of a normal initial diastolic pressure and a rapid rise in pressure toward the end of diastole. A characteristic third heart sound can be seen as the pressure begins to rise in diastole. (From Moscovitz, H. L., *et al.*: An Atlas of Hemodynamics of the Cardiovascular System, 1963. Reprinted by permission of author and Grune and Stratton Co., Inc., N. Y.)

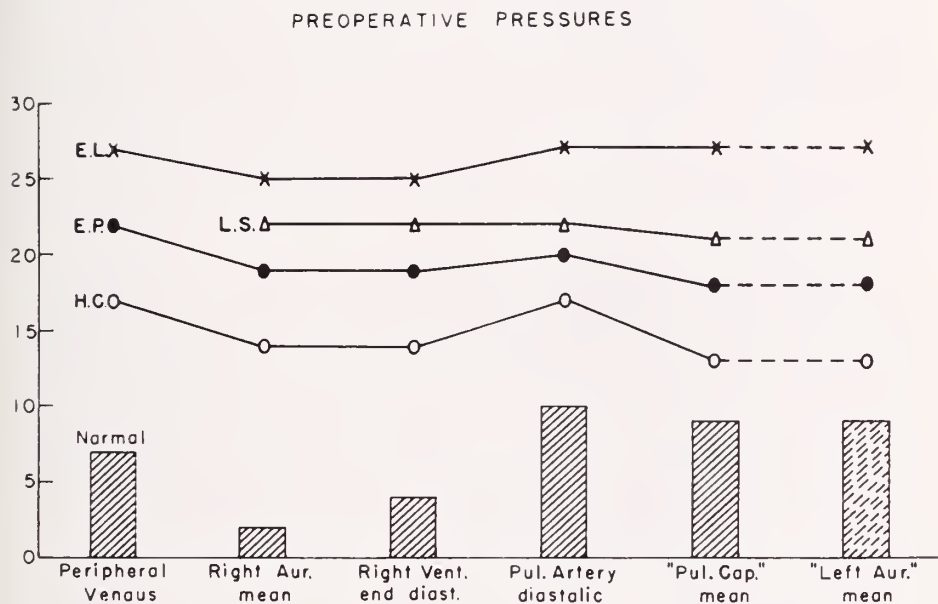


FIG. 9. Intravascular pressures in patients with constrictive pericarditis. There is an elevation of both left and right atrial pressures, indicating that compression of both ventricles occurs. (From Sawyer, C. G., *et al.*: Am. Heart J., 44: 207, 1952. Reprinted by permission of C. V. Mosby Co., Inc.)

diastole with the production of a very high end-diastolic pressure. This is due to the inability of the restricted right ventricle to receive a considerable volume of blood without a pressure rise and may occur in intrinsic myocardial disease as well as in restriction due to pericardial compression. From tracings

recorded by the intracardiac phonocatheter, it can be seen that the third heart sound is noted as the pressure begins to rise in diastole, probably because of filling of this restricted chamber.

Finally, as shown in Figure 9, study of hemodynamic abnormalities in constrictive pericarditis indicates that compression of both ventricular chambers occurs with resultant rise in both right atrial and left atrial pressures. This makes it important for the surgeon to achieve the widest possible decortication.

SUMMARY

The functions of the normal pericardium and the hemodynamic effects of pericardial disease are described.

The normal pericardium limits excessive cardiac dilatation, helps to maintain adequate response of the cardiac output to increasing inflow loads and therefore an appropriate "Starling curve." In addition, it promotes adequate cardiac output response to changes in heart rate and limits undue displacement of the heart.

The dynamic alterations produced by pericardial effusion are closely related to the speed of accumulation of the fluid. It has been demonstrated that when intrapericardial pressure is increased to a critical level, there may be impedance to diastolic ventricular filling, a rise in left and right atrial pressure, a diminution in cardiac output and eventually a precipitous fall in arterial pressure. These changes may be accentuated by premature closure of the A-V valves, which further diminishes fiber length and hence, stroke volume. In addition, there is presumptive evidence of diminution in coronary flow with resultant deterioration of the function of both right and left ventricles. This function may be restored to some extent by the administration of vasopressor agents.

The hemodynamic features of constrictive pericarditis are reviewed. It is seen that the rapid rise in ventricular pressure to high level at the end of diastole is related to an inability of the restricted right ventricle to receive a considerable volume of blood without a pressure rise. Intracardiac phonocardiography has demonstrated that the frequently heard third heart sound in constrictive pericarditis occurs as the pressure begins to rise in diastole, probably because of filling of the restricted chamber. Hemodynamic studies in constrictive pericarditis have demonstrated that compression of both ventricles occurs with resultant rise in both right and left atrial pressures.

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Radiotherapy in Angina Pectoris: A Controlled Study

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INTRODUCTION

In recent years, there have been many attempts to increase the blood supply of the myocardium in patients who have coronary arterial disease. The approaches have been primarily surgical and consist of using a foreign irritant, tissue graft, endarterectomy, and various anastomotic and implantation procedures involving systemic vessels and the coronary arteries. Each method has enjoyed its period of popularity, only to be discarded by the new rival method, and today there is no wholly satisfactory method of replacing the diseased coronary vessels.

In an attempt to obtain the same protective benefits of myocardial revascularization without the necessity of surgical intervention, the use of cardiac irradiation as a therapeutic method was proposed and investigated.

RADIATION EXPERIMENTS ON THE DOG'S HEART

In the Surgical Research Laboratory of The Mount Sinai Hospital a number of experiments were performed studying the effect of irradiation on the coronary blood flow (1-4). Doses of 1300 rads, 2000 rads, and 2500 rads were given to the myocardium of mongrel dogs in three to five sessions of treatment over a two and a half week period. The dogs survived the treatment without noticeable effect. At varying intervals (from one week to six months) following the radiation, each dog was subjected to thoracotomy and the coronary circulation was studied. It was found that 8 per cent of unirradiated animals survived ligation of the left circumflex coronary artery, and that 11 per cent survived ligation of the anterior descending coronary artery. In contrast, in the animals previously irradiated, 40 per cent of the dogs survived ligation of either vessel at one week after therapy. At six months after therapy, 75 per cent survived ligation of the anterior descending coronary artery. These surviving irradiated dogs exhibited a better anastomotic flow, as demonstrated by measuring blood flow in the vessel distal to the point of ligation. The increased anastomotic flow was also demonstrated by injection of the coronary arterial tree with barium and with plastic preparations (Fig. 1). Electrocardiographic (4) and pathological (5) study of the irradiated heart revealed no evidence of damage either to the cardiac musculature or to the coronary ves-

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sels. The mechanism of induced increased collateral circulation is still unclear and a subject worthy of further laboratory study. The present report explores the possible clinical application of the effect observed.

PILOT CLINICAL STUDY

The logical application of the experimental finding would be to irradiate the heart of healthy individuals who would be prone, on account of their family history, their age, occupation, blood pressure and cholesterol levels, to suffer from coronary occlusion. The irradiation should offer some protection against fatality if and when an occlusion occurred. Such a study was not

TABLE I
Professor MacMahon's Summary of Detailed Results Submitted to Him

	Irradiated	Control
Original group	19	19
Omitted	2	2
Cases to be studied	17	17
Assessed by E. S.		
Dead by June '61	3	3
Not examined	0	3
Examined June '61	14	11
Improved	5	3
Questionable	3	3
Not improved	6	5
Assessed by H. J.		
Dead by Nov. '61	3	3
Not examined	2	5
Examined Nov. '61	12	9
Improved	3	3
Questionable	2	0
Not improved	7	6

undertaken, first, because we felt that the laboratory evidence was not conclusive enough to warrant offer of the treatment to a healthy individual; and secondly, because such a study would involve hundreds of volunteers and would, of necessity, be a very long-term statistical study. Instead, patients with severe angina pectoris were treated. It was postulated that small doses of radiation would produce dilatation of existing myocardial capillaries and precapillary arterioles which, in the presence of myocardial ischemia, would persist and increase in number because of the observed ability of cardiac tissue to develop collaterals. There was also some precedence for this type of trial, since the irradiation of the precordial area and of the cervical sympathetic chain in patients with angina pectoris had been tried by several investigators, some as early as 1916 (6).

A group of 25 patients was selected. Each patient was disabled by severe

angina of long duration. In many cases, there had been multiple coronary occlusions. The tolerance of the heart to irradiation has been studied in recent years (7-9). From these reports, it was concluded that a dose of 2000 in two weeks might cause temporary electrocardiographic changes, but otherwise would be completely safe as far as permanent damage to the heart is concerned. Accordingly, each patient was treated by a single anterior precordial field of cobalt⁶⁰ radiation at 50 cm SSD. In ten sessions, in an overall time of two weeks, a peak dose of 2000 rads was delivered. There was no untoward effect of irradiation in this group and the results ranged from no improvement to moderate or marked improvement when the patients

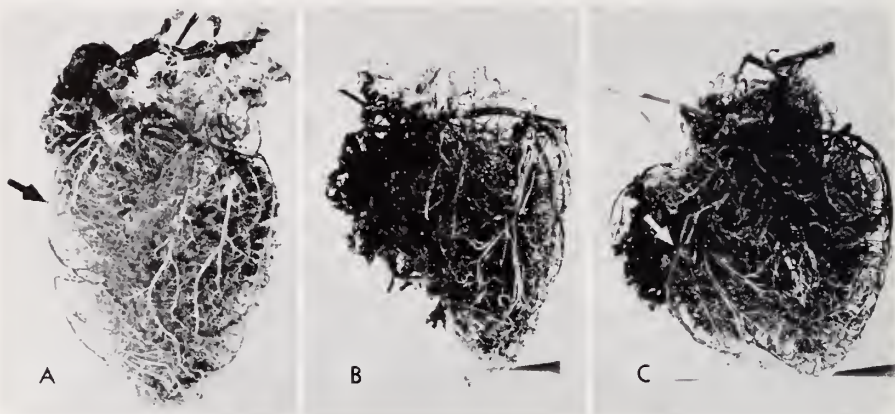


FIG. 1A. Vinylite injection and corrosion specimen of normal coronary circulation of the dog (lateral view). Arrow points to the anterior descending coronary artery.

FIG. 1B. Specimen of non-irradiated heart one-half hour post ligation of the anterior descending coronary artery. Note segment of absent coronary circulation which corresponds to distribution of the ligated vessel.

FIG. 1C. Specimen of irradiated heart one-half hour post ligation of the anterior descending coronary artery. The pattern of vascularity resembles a normal heart without vessel ligation. The anterior descending coronary artery (arrow) has filled in a retrograde fashion by means of functioning intercoronary anastomotic channels.

were evaluated at intervals during the next eighteen months. We were distinctly encouraged by this preliminary experience and decided to embark on a controlled clinical test.

RANDOM SELECTION CLINICAL TRIAL

There is great difficulty in assessing the efficacy of any therapy in a patient with severe angina pectoris. First of all, there is the natural variability of the patient's clinical status from month to month. There is no good laboratory test to show the adequacy of cardiac circulation at any time. Further, these patients are prone to suggestion, and any treatment offered has a placebo effect in a minority of the patients. For criteria of improvement, one can only have a subjective evaluation of the amount of pain which the patient experiences, the number of nitroglycerin tablets that he takes per

dium, and the amount of physical exercise which he can do without inducing angina. A trial was therefore designed in such a way that half of the patients would act as controls. These control patients had every procedure, including a mock treatment under the cobalt machine in exactly the same way as the irradiated patients.

Thirty-eight patients participated in the study. The group consisted of both private and clinic patients. The duration of the illness ranged from four months to nineteen years, the average being seven years. No patient was treated during or shortly after an acute coronary occlusion. All patients were refractory to standard therapies and had persistent angina of varying degrees. Three patients had previously undergone radioactive iodine ablation of the thyroid. One patient had had an internal mammary ligation, and one patient had had a thoracotomy with installation of talc in the pericardial sac. The ages ranged from 40 to 79 years, the average being 59. Thirty-one patients had 42 previous hospitalizations for coronary artery disease. Twenty members of this group had 26 hospitalizations for documented infarction, and eleven members had 16 hospitalizations for coronary insufficiency or severe angina. The severity of the disease ranged from angina on moderate effort to angina decubitus. Nitroglycerin requirements were from zero to 30 tablets per day. Several patients also required narcotics. Thirty-six were ambulatory, and two were hospital in-patients.

Each patient was interviewed and examined. An electrocardiogram, chest x-ray and blood cholesterol level were obtained. Care was taken to exclude patients in whom the pain might be due to some other cause, such as a hiatus hernia or anemia. To each patient it was explained that he would receive ten sessions of cobalt therapy and that the amount of treatment given would cause him neither local nor systemic reaction and was safe as far as long-term effects were concerned. It was also explained that the method of treatment was under trial and no assurance was given that their clinical condition would certainly improve. Patients were unaware of the double blind aspect of the study, and, in the case of private patients, so was the referring physician. The sample of 38 patients was stratified into clinic and private status patients and, within each group, selection as a control or as a treated patient was made in a random manner.

Each patient had a localization x-ray film to insure that the anterior field of radiation covered the whole of the heart. In general, a field 13×13 cm was adequate, and from this the superior lateral quadrant was leaded off to correspond with the left border of the heart. Each patient was set up under the therapy apparatus by a radiotherapist. In the irradiated group, a peak dose of 2250 rads was delivered in ten equal fractions over a two-week period. The control patients lay under the machine for an equal length of time and the shutter was opened and closed instantaneously at the beginning and end of the prescribed time. Neither the radiotherapist nor any of the physicians in clinical contact with the patient knew whether the patient had been exposed to radiation or not. This information was available only to the Direc-

tor of the Department of Radiotherapy and the Senior Radiotherapy Assistant who controlled the exposure period. Since there was no systemic or local reaction, the physicians could not distinguish control from treated patients.

RESULTS

All the patients were followed for at least twelve months and, on the average, were interviewed six times during this period. Subjective and objective observations were recorded. The nitroglycerin intake, the walking tolerance, the frequency and duration of angina attacks, and the patient's ability to work, were the factors recorded. Repeated electrocardiograms and blood cholesterol levels were done and showed no significant change from the pretreatment records. Patients were told that the purpose of the interview was to evaluate their clinical condition, and they continued to visit their private or clinic physicians. Independent assessments were made by two of the authors (E. S. and H. J.). When the final assessments had been made, the key to the study was opened, making available which patient received the radiation and which did not. The individual assessments were submitted to Professor Bryan MacMahon of the School of Public Health, Harvard University, and we are indebted to him for the tabulation (Table I). We are also indebted to Professor MacMahon for the following commentary: "It needs no statistical test to determine that 3 deaths out of 17 in each series represent no significant difference, or that 5 improvements out of 15 do not differ significantly from 3 out of 11; however, neither can it be said that no difference exists; it can only be said that no difference has been demonstrated. This is a small numbers problem and there's nothing to be done about it other than to wait until more patients die, increase the series, or preferably, both."

Notwithstanding the difficulty in assessing the patients with angina pectoris, it was remarkable that there was such a degree of agreement between the two independent assessors. No harmful effects of irradiation were observed either during the administration of the treatment nor in the follow-up period.

DISCUSSION

This trial illustrates the necessity, when studying patients with angina pectoris, of having a strictly controlled trial with adequate numbers of patients. It is interesting that as many as six out of eleven control patients admitted to some improvement following the procedure. This improvement must be related to the natural variability of the anginal syndrome and to the psychological effects of simulated therapy. In retrospect, it is obvious that the sample was much too small. This was partly because we did not expect to have such a high proportion of improvements in the control group. Two patients exhibiting the best response are worthy of commentary. One 70 year old female with angina pectoris of five years' duration and one hospitalization for myocardial infarction, two previous courses of iodine therapy, received cardiac irradiation and was considerably improved one year later. Another patient, a 53 year old male with two infarctions and angina pectoris of ten years' duration, was dramatically improved and continued to be so during

the following year. This patient was in the control group. These two cases again illustrate the difficulty in obtaining accurate evaluation of therapy for the relief of angina pectoris and coronary disease.

Whatever be the effect of irradiation on the coronary vessels of patients with angina, it cannot be shown to relieve all of the symptomatology in this small group of patients. This group of patients had chronic advanced coronary artery disease over a prolonged period of time. The degree of myocardial pathology in this group may have been such that a maximum collateral circulation had already been established. Whether the effect of radiotherapy on the muscle is to reduce the catecholamine-induced metabolic hypoxia as suggested by Raab (10) remains to be seen. In the past, irradiation of the adrenals had been used with this in mind.

This study also demonstrates the necessity of having objective evidence of improvement in the blood supply to the heart, in addition to the usual subjective evaluation. Coronary arteriography, demonstrating a definite increase in the collateralization of the blood supply would, of course, have much significance in the final evaluation of the result. The existence of a placebo effect cannot be stressed too frequently. Without objective evidence of improvement of blood supply, a study without a double blind methodology cannot be taken too seriously. As has been shown in this study, no difference has been demonstrated between the controlled and irradiated groups. This does not necessarily mean that a difference does not exist. A follow-up of both groups for several years may show the difference, if any. One cannot deny the experimental evidence of a difference between irradiated and non-irradiated animals. Whether a common effect is produced by anti-thyroid therapy, sympathectomy and irradiation of the heart, is a study worthy of consideration.

SUMMARY AND CONCLUSIONS

1. A group of 38 patients with angina pectoris was selected for a controlled study of the effect of radiotherapy on the angina.
2. The study was so designed that half the patients would act as controls. These controls had every procedure in exactly the same way as the treated patients.
3. All patients were followed for at least twelve months.
4. One observer noted improvement in 14 out of 25 patients examined at 12 to 19 months following true or mock therapy.
5. No difference between the irradiated or control groups could be demonstrated.
6. The need for controls in the study of therapy for angina pectoris is emphasized.
7. There was no deleterious effect of cardiac irradiation during or following the administration of the therapy.

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A Clinical Study of Cerebral Vascular Malformations

(The Significance of Migraine)

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Although pathologic description of vascular malformations of the brain may be dated from Virchow (1), the earliest major formulation was made by Cushing and Bailey in 1928 (2). It is felt that the earlier distinctions between venous and arteriovenous malformations should be abandoned (3). It is, therefore, with the broad group of vascular malformations that this report will deal. Such malformations were considered to be quite rare in earlier reports from several neurosurgical centers (2, 4, 5). More recently, the introduction and widespread use of arteriography has permitted the more adequate delineation of the clinical entity (6-9).

During the period 1949-1962, 65 patients were seen in whom the presence of an arteriovenous malformation presented a problem in diagnosis and management. Classification of these cases in terms of the patients' initial symptoms is contained in Table I and includes subarachnoid hemorrhage, focal seizures, generalized seizures, other neurological signs and symptoms and "vascular headache of migraine type."

Note has often been made of the presence of migraine type syndrome in these cases (10-15). It has been suggested that the malformation, if posteriorly placed, may simulate migraine syndrome, and that the connection between the vascular malformation and migraine has been presumed to be a causative one. It is with particular interest in this relationship, and in the prognosis of those patients with subarachnoid hemorrhage, that this study was undertaken.

The headache group has been delineated in accordance with the suggestion of the Ad Hoc Committee on Classification of Headache, Research Advisory Council, National Institute of Neurological Disease and Blindness (16). The "vascular headache of migraine type" thus includes patients with both "classic" migraine and "common" migraine or "sick" headache. The former would describe recurrent attacks of headache, commonly unilateral, associated with anorexia or sometimes nausea and vomiting, with sharply defined transient visual and other sensory or motor prodromata, or both. The latter group would not have striking prodromata and would less often be unilateral.

There is no significant sex difference in this series. The earliest onset of symptoms was at age two, and the latest at age sixty-two. Symptomatology may, therefore, appear rather late despite the presumably congenital nature of the malformation. A malformation may indeed enlarge with increasing age (17). Case #11 with focal seizures (Table III) illustrates this. A carotid

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arteriogram failed to demonstrate a malformation initially, but did so when repeated one year later.

GROUP A. SUBARACHNOID HEMORRHAGE

Thirty-four (52%) of the 65 patients first presented with subarachnoid hemorrhage (Table II).

The usual presentation was that associated with intracranial bleeding of any cause. Focal neurological signs were found in 22 cases (65%). Of these 22 cases, 11 had intracerebral hematoma demonstrated by arteriography or surgery. Focal abnormalities on electroencephalogram were found in these 22 cases. In patients #20 and #29 there were no localizing signs, but the electroencephalogram correctly localized the malformation as later demonstrated on arteriography.

No attempt was made to separate deeply placed from more superficial mal-

TABLE I
Age at Time of Initial Symptoms (In Retrospect)

	Total	0-9	10-19	20-29	30-39	40-49	50+
Group A: Subarachnoid hemorrhage.....	34	2	8	8	6	7	3
Group B: Focal seizure.....	14	1	2	2	8	2	0
Group C: Generalized seizure.....	6	1	2	1	1	1	0
Group D: Other neurological signs and symptoms.....	5	0	1	1	3	0	0
Group E: Vascular headache—migraine type.....	6	0	4	1	1	0	0
Total.....	65	4	17	13	19	10	3

Male—30.

Female—35.

formations. It is frequently not possible to delineate the full extent of the malformation by arteriography.

Treatment in these cases cannot be evaluated adequately because of the small number of cases. Sixteen of these 34 patients underwent surgery. Four of these who did so were patients with intracerebral hematoma. One patient underwent carotid ligation while in extremis. Cases #23 and #28 had intracerebral hematoma as demonstrated by arteriography, but did not require surgery.

GROUP B. FOCAL SEIZURES

Except for the presence of intracranial bruits in three cases (#6, #12, #13), the fourteen patients with the initial symptom of focal seizures (Table III) generally could not be differentiated from those whose focal seizures were due to another etiology. Postictal focal phenomena were present in four (30%) out of the 14 cases (#4, #9, #11, #13). Eleven out of the 12 cases which had electroencephalography had findings consistent with the focal quality of their

symptoms. Case #10, which had bitemporal slowing, left greater than right, had a large collection of veins at the conjunction of the straight sinus and great cerebral vein.

One patient (#13) developed spontaneous hemorrhage following a six-month history of focal seizures. Case #14 had an aura quite similar to that of "migraine." He had episodes of "colored lights" in front of both eyes, followed by headache with nausea. Occasionally, he would then go on to feel a squeezing sensation in his "stomach," his head would turn to the right, and he would have a generalized convulsion. This patient had a temporal-occipital malformation.

GROUP C. GENERALIZED SEIZURES

Of the six patients with the initial symptom of generalized seizures (Table IV), case #5 had postictal focal weakness. Case #2 had calcification on plain skull x-ray. Case #3 had spontaneous subarachnoid hemorrhage after a fourteen-year history of seizures.

GROUP D. OTHER NEUROLOGICAL SIGNS AND SYMPTOMS

Three of the five cases (Table V) presented with homonymous field defects. Two (#1 and #3) later developed spontaneous hemorrhage. Case #5 was the only case in the entire group of 65 that presented with a bruit alone.

GROUP E. VASCULAR HEADACHE

It is with the group of vascular headaches that we shall deal in some detail.

1. D.H., (F). Since age 10, episodic headache at first one to two times per year, then much less frequent. Pain would start on left side of head, then over O.S., followed by loss of vision in upper field, and then nausea and vomiting. Entire episode would last several hours. At age 23, she began to have episodic twitching of the right cheek with numbness. When 31, she had four-hour episode of staring and "silly speech." Two years later, she began to have recurrent episodes during which "wrong words came out" and shaking of right-sided extremities. Neurological examination was normal. Spinal fluid clear, protein 37 mg%. Electroencephalogram slow activity, mainly left, anterior temporal. There was an egg-shaped calcification on skull x-ray 1½ inches superior and posterior to dorsum sellae on left. Left carotid angiogram showed large malformation in area of the calcification filling from middle cerebral artery, filling from right side as well. Pneumoencephalogram showed deviation of the left temporal horn toward the midline and shift of the left lateral ventricle to the right. Patient is now 36 and asymptomatic.

2. M.K., (F). As schoolgirl, she had episodic blurring of vision in right field with lightning flashes associated with frontal headache, followed by nausea and vomiting. Negative family history for migraine. At age 17, she had first of a series of spontaneous subarachnoid hemorrhages, eventually totaling eleven. These were characterized by photophobia and stiff neck, and loss of consciousness. There was a hiatus between age 28 and 43. The episodes had become less

TABLE II
Group A. Patients Presenting with Subarachnoid Hemorrhage

No.	Name, Sex	Age	Clinical History	EEG	X-Ray	Treatment
1	N.G. M	26	Sudden onset of headache, loss of consciousness; spinal fluid bloody.	Frontal temporal slow wave bursts, right greater than left.	Malformation right posterior frontal area filling from left carotid circulation as well.	Craniotomy—malformation excised.
		28	Developed a left hemiparesis and an organic mental syndrome; spinal fluid normal.			
		35	Severe hemiparesis, grand mal seizures, unable to care for self.			
2	A.M. F	16	Subarachnoid hemorrhage.	Diffuse slow wave bursts, left greater than right, most marked frontally.	Left thalamic malformation. PEG; increased size of ventricles and defect in floor of lateral ventricle.	Craniotomy—coagulation of feeding arteries. Repeat arteriogram normal.
		40	Sudden headache, right hemiparesis, aphasia. Bruit over left carotid artery. Bloody spinal fluid.			
		46	Well.			
3	L.K. F	16	First of 35 episodes of hemorrhage into subarachnoid space.	Slow wave bursts posteriorly; right greater than left.	Malformation right parietal area filling from anterior and middle cerebral arteries <i>bilaterally</i> .	Right carotid artery ligation following 21st hemorrhage.
		41	Mild left hemimotor-sensory syndrome, particularly involving hand. Spinal fluid xanthochromic.			
		43	Re-bled and died.			
4	B.W. F	50		Left temporal slow wave bursts.	Pineal shifted to right. Left carotid angiogram showed large temporal lobe mass and malformation.	Craniotomy—intracerebral clot evacuated and anomaly excised.
		32	Sudden onset on left temporal pain, loss of consciousness; subsequent aphasia, right hemimotor-sensory syndrome including homonymous hemianopsia; spinal fluid bloody.			
		36	Slight dysphasia.			
5	E.G. F	42	Loss of consciousness following history of "peculiar head sensation" for several weeks. Examination revealed a right homonymous quadrantanopsia and aphasia; spinal fluid bloody.	Bitemporal slow activity.	Temporal lobe intracerebral hematoma and malformation in right frontal temporal area filling via left carotid artery. Right carotid angiogram <i>normal</i> .	Craniotomy—anomaly excised.
			Follow-up: doing well.			

6	H.W. F	36	Sudden onset of headache and coma. Bilateral blurred optic discs. Spinal fluid bloody.	Normal.	Left frontoparietal malformation fed by supracallosal branch of anterior communicating; anomalously penetrated into corpus callosum and drained into internal cerebral vein.	Partial closure of left common carotid artery.
7	J.M. F	46	Well.			
		17	Sensory and motor "Jacksonian seizure" right arm to leg to face. Aphasia with right hemimotor-sensory syndrome. Spinal fluid bloody.			
		27	Slow recovery, mild hemiparesis, arm more than leg.			
8	M.F. F	45	Subarachnoid hemorrhage.	Left cerebral dysfunction.	Malformation in posterior left cerebral hemisphere, feeding into vein of Galen.	Craniotomy—hematoma evacuated, feeding vessels clipped.
		49	Follow-up: right homonymous hemianopsia, organic mental syndrome and grand mal convulsions. Severe depression. Institutionalized.			
9	R.D. M	13 15	Began to have nonspecific headaches, not very severe. Acute occipital headache and lethargy. Had left central facial weakness and left Babinski sign. Spinal fluid bloody.	Diffuse cerebral dysfunction.	Right carotid angiogram, malformation in posterior frontal region of basal ganglia, fed from anterior choroidal and lenticular striate vessels.	In extremis. Left carotid artery ligation performed. Patient died.
10	O.A. F	39 41	Symptoms improved, but rehospitalized several months later in coma; bloody spinal fluid.			
			Severe progressive headache of ten days' duration, left hemiparesis, papilledema. Spinal fluid bloody.	Diffuse slow activity, right hemisphere.	Small malformation in midportion Sylvian vessels on right.	Right common carotid ligation.
			Subarachnoid hemorrhage.			Craniotomy—evacuation of hematoma in right temporal lobe. Patient died.
11	S.B. F	28	Acute pain in right eye and temple. Spinal fluid bloody.		Large malformation in left mid-parietal area, filling from right carotid circulation. Left carotid arteriogram normal.	Right common carotid ligation.
		34	Has severe right-sided headaches occurring monthly.			
12	J.G. M	53	Sudden onset of an organic mental syndrome and right hemiparesis. Spinal fluid bloody. Follow-up: residual aphasia.	Left cerebral dysfunction accentuated in temporal occipital area.	Hematoma and malformation of anterior temporal lobe.	Craniotomy—hematoma evacuated and anomaly excised.

TABLE II—Continued

No.	Name, Sex	Age	Clinical History	EEG	X-Ray	Treatment
13	R.B. M	17	Sudden left supra-orbital headache followed by stupor, right hemiparesis, and hemianopsia. Spinal fluid bloody.	Diffuse cerebral dysfunction. Left occipital temporal slow wave focus.	Multiple calcifications. Left carotid arteriogram demonstrated avascular mass in temporal lobe.	
		19	Episodes of flushes of right side of face and staring 4 to 5 times a day. Next year noted shaking of left arm during these spells.			
		20	Severe headache. Bilateral papilledema. Spinal fluid xanthochromic.	Left cerebral dysfunction.		
		22	Rapid onset of inability to hear and then stupor. Spinal fluid bloody.	Diffuse cerebral dysfunction with focal accentuation left temporal occipital area.		
14	Z.T. F	23	Episodic deafness lasting around 20 minutes, then acute headache and right hemiparesis. Spinal fluid bloody. Died.		Avascular left temporal lobe mass.	Craniotomy—hematoma evacuated. Biopsy—angioma.
		20	Six-week history progressive right-sided headache radiating down neck. Developed aphasia and an organic mental syndrome. Spinal fluid xanthochromic.	Left temporal lobe slow wave focus.		
15	J.B. M	15	Sudden onset right hemiplegia and aphasia.		Malformation left posterior frontal parasagittal near surface; avascular mass.	Craniotomy—hematoma evacuated.
16	M.R. M	70	Acute severe headache, stupor. Left hemiparesis. Spinal fluid bloody.	Left-sided slow wave; with spikes left motor.	Pineal shifted to right. Left carotid angiogram—avascular temporal posterior mass.	Craniotomy—hematoma evacuated; abnormal blood vessels. Patient died.
17	R.J. M	25 27 29	Headache, stiff neck. Headache and bradyphrenia. Spinal fluid bloody. Headache, somnolence, right hemiparesis; spinal fluid xanthochromic.		Right carotid angiogram showed malformation of vein of Galen. Right and left carotid angiograms showed malformation of vein of Galen, as did vertebral arteriogram. Pneumoencephalogram—hydrocephalus and 4th ventricle pushed back.	Radiotherapy.
		30	Died.			

18	C.C. F	38	Had acute onset severe left-sided headache with progressive aphasia. Spinal fluid xanthochromic.	Severe left frontotemporal slow activity greater than right frontal, diminished alpha on left.	Left carotid angiogram—malformation mid-parietal area.	Radiotherapy.
19	S.D. F	46	Well.		Right parietal calcification one inch from inner table. Right carotid angiogram—right parietal area malformation.	None.
20	R.L. M	33	Developed severe generalized headache; spinal fluid bloody.			
		47	Has had approximately 6 subarachnoid hemorrhages without residua. Well.			
21	C.M. F	46	Headache, stiff neck, organic mental syndrome. Spinal fluid bloody.	Diffuse abnormality, left frontal temporal slowing.	Left carotid arteriogram—frontal lobe malformation. Right carotid arteriogram revealed lesion filled by way of anterior communicating artery.	None.
		50	Well.			
22	T.J. F	46	Acute onset of headache, coma, right hemimotor-sensory syndrome. Spinal fluid bloody.	Left cerebral dysfunction accentuated in temporal region.	Malformation in anterior medial portions of temporal lobe receiving circulation from left middle cerebral, posterior cerebral and posterior communicating arteries. Lesion also visualized by right carotid arteriography.	None.
			Follow-up: improving slowly.			
23	W.M. M	25	Sudden severe left-sided headache and loss of consciousness, then aphasic. Spinal fluid bloody.	Left posterior temporal and occipital slow activity.	Malformation left, filling inferiorly from left middle cerebral artery.	None.
		20	Sudden onset of right supra-orbital headache and numbness and weakness of left upper extremity and left face, with leg less severely involved. Spinal fluid xanthochromic. Port wine anomaly on anterior chest wall.	Focal slowing in right temporal region.	Right carotid arteriogram—intracerebral hematoma and vascular malformation 2 to 3 cm below cortex, fed from ascending frontal and parietal branches of middle cerebral artery.	None.
		22	Follow-up: fine.			
24	L.F. F	16	Severe frontal headache, stiff neck, trouble seeing to left. Left hemiparesis and homonymous hemianopsia. Spinal fluid bloody.	Diffuse slow waves, right more than left.	Vertebral arteriogram—malformation in right occipital area. No filling by right carotid arteriography.	None.
		18	Well.			

TABLE II—Continued

No.	Name, Sex	Age	Clinical History	EEG	X-Ray	Treatment
25	I.R. M	62	Sudden severe headache. Had had diminished hearing A.D. with buzzing sound in ear for past year. Bruit heard. Spinal fluid bloody.	Nonspecific, mildly diffuse abnormality.	Right carotid arteriogram—malformation right posterior fossa.	None.
26	D.S. F	43 50 51	Episode of stupor; questionably related to being hit on head by stone. Spinal fluid bloody. Spontaneous headache and progressive stupor. Spinal fluid bloody. Later that year, recurrence with right hemiparesis. Spinal fluid bloody. Severe occipital pain followed by right hemiparesis. Bruit over right carotid artery. Spinal fluid bloody. Died.	Bilateral slow wave bursts, right more than left.	Left parietal area malformation in distribution of middle cerebral artery fed by both carotid arteries.	None.
27	D.B. F	44 46 47	Severe headache, unable to speak and loss of consciousness. Bloody spinal fluid. Sequelae—episodes of numbness of left hand. Severe pressure left temple, rendered unconscious. Spinal fluid clear. Grand mal once yearly.		Left carotid arteriogram—parietal area malformation, also fed by right carotid circulation but not from vertebral basilar vessels.	None.
28	A.O. M	10 13	Headache, loss of consciousness, right homonymous quadrantanopsia. Spinal fluid bloody. Follow-up: recovered with some quadrant defects remaining.	Diffusely abnormal, left more than right.	Intracerebral hematoma with malformation on left.	None.
29	H.G. M	9 15 16	Severe occipital headache, in coma for several days. Episodic "automatic" behavior with salivation. At other times, would see "light bulb" in front of right eye, associated with a "strange sensation." Poor school work. Antisocial behavior.	Left temporal lobe focal bursts of slow activity.	Large malformation left parietal lobe, fed by left anterior cerebral and middle cerebral arteries.	None.

30	S.D. F	25	Severe headache, rendered unconscious. Spinal fluid bloody. Since then, episodic dream states. She would see a place where she had formerly worked "as though it were a little movie." Also, transient attacks of "jerking" of right extremity. Admitted for investigation. Right homonymous superior quadrantanopsia.	Left temporal focal slow wave bursts.	Malformation between terminal portion of middle cerebral artery and posterior cerebral artery, fed by posterior cerebral artery.	None.
31	M.C. F	34	Sensory-motor seizure of right arm and hand, followed a week later by stupor and right hemiparesis. Spinal fluid bloody.		Malformation arising from left anterior and middle cerebral artery fed from right carotid artery as well as the left carotid artery via anterior communicating artery.	None.
32	K.K. F	40	Slight right hemiparesis.			
		8	Had injury, became listless and vomited; weakness right upper extremity; dystaxia with head tilted to right. Spinal fluid xanthochromic. Improved.			
		9	Sudden severe headache with somnolence, eyes divergent. Spinal fluid bloody. Died on the next day. Post mortem—venous malformation of right cerebellum.			
33	A.B. M	42	Six-month history of intermittent severe right-sided headache. Two weeks prior to hospitalization, numbness of right side of face. Admitted because of sudden loss of consciousness. Spinal fluid bloody.	Normal.	Right carotid angiogram—malformation in posterior fossa. Midline at level of mastoid. Did not fill by way of vertebral artery or left carotid artery.	None.
		43	Episode of unpleasant cold sensation in left leg radiating distally and up to chest wall, which persisted. Then developed a cold sensation in left arm.			
		44	Sudden numbness left side of body and pain in neck. Noted to have severe bilateral involvement of pons and medulla. Spinal fluid xanthochromic. Residual left hemisensory-motor syndrome.	Normal.	Filling of malformation in posterior fossa as before.	

TABLE II—Continued

No.	Name, Sex	Age	Clinical History	EEG	X-Ray	Treatment
34	J.R. M	16	Headaches nonspecific.	Normal.	Left carotid angiogram—malformation left frontal pole filling from both anterior and middle cerebral arteries. Also filled from right carotid artery. Right brachial arteriogram normal, but after each injection complained of figures in left field and also flashing lights. At one injection complained of inability to see hand in left temporal field; after last injection complained of jugged, wavy line in <i>right</i> field of vision.	
		27	Six-month history of intermittent left temporal head pain. Acute onset of severe headache with stiff neck. Ten minutes later, "v" shaped scintillating figure left field of vision, then only in left eye, with blurring of vision in that eye. Attack lasted five minutes. Noted eyeball tenderness. Spinal fluid bloody.			
		28	Acute onset of headache and again had "v" shaped lights in left field of vision lasting several hours. Spinal fluid bloody.			

severe recently, but she did have an episode of speaking irrationally. On admission (age 47), her neurological examination was normal. Spinal fluid was xanthochromic, protein 161 mg%. Electroencephalogram was normal. During hospital stay, she had spontaneous subarachnoid hemorrhage with right hemiparesis and homonymous field defect. A left brachial arteriogram filled malformation in left parietal region, as did right carotid angiogram. She remains well now, age 48.

3. M.A., (M). Age 37, began to have recurrent left-sided headaches with sensations of swelling in left temporal region, lacrimation of O.S., and stuffiness of nose. He had difficulty reading. He would occasionally see rainbows around lights. Would occasionally have associated nausea. Episodes would last several hours. They continued until age 43, but he was then asymptomatic until age 44, when they recurred. On neurological examination, he had blurred discs bilaterally and right homonymous hemianopsia. Electroencephalogram showed slowing in left temporal occipital region. Spinal fluid colorless; pressure 240; protein 35 mg%. On arteriography, left carotid filled malformation extending from posterior frontal to occipital area, extending from midline to periphery. Middle cerebral and anterior cerebral arteries were not well delineated. No follow-up.

4. L.F., (F). Age 18, left-sided headache preceded by blurring of vision, followed by nausea and vomiting. Age 19, had spontaneous subarachnoid hemorrhage. There was temporal occipital slowing on left on electroencephalography. Spinal fluid was normal. Left carotid filled small temporal occipital malformation from parietal branch middle cerebral artery, as well as from posterior cerebral artery. Now, at age 21, she has continued to have left-sided headache two to three times per month, preceded by blurring of vision, followed by vomiting.

5. V.D., (F). Age 19, began to have monthly throbbing left-sided headache associated with spots before eyes and lacrimation of O.S., with nausea and vomiting. One such episode lasted an entire week. At 29, she had begun to have episodes of loss of consciousness. She has also had episodes of incoherent mumbling speech. On examination, she had a right homonymous quadrantanopsia, superior quadrant greater than inferior. Bruit was heard over each eye and in the neck bilaterally. Spinal fluid was clear, protein 29 mg%. There was slow wave activity left anterior leads. Left carotid filled malformation in temporal occipital area. Now, age 33, she continues to have monthly seizures.

6. J.C., (M). Had left-sided headaches for many years. Age 43, had loss of consciousness. Age 44, admitted for severe occipital headache. Had right homonymous hemianopsia. There was diminished alpha voltage and percentage time on left. Spinal fluid was normal. Left carotid arteriogram filled large a-v malformation. Now, age 45, he continues to have headaches, but is otherwise well.

Two cases (§2 and §4) subsequently developed subarachnoid hemorrhage. Cases §1 and §5 developed focal seizures. In the two remaining cases, headache was the presenting complaint. Both these patients, on neurological examination, had homonymous hemianopsia. Electroencephalography was local-

TABLE III
Group B. Patients Presenting with Focal Seizures

No.	Name, Sex	Age	Clinical History	EEG	X-Ray	Treatment
1	W.H. M	38 41	Episodic right-sided weakness and difficulty with speech followed by loss of consciousness. Admitted for investigation, neurological examination normal.	Increased alpha amplitude, diminished frequency in left temporal parietal region.	Left carotid angiogram—left parasagittal lesion. Repeat left carotid angiogram after surgery—parietal malformation fed by anterior cerebral artery.	Craniotomy—negative exploration; anticonvulsants.
2	F.M. M	51 51 53	Monthly focal seizures. Episodes of twitching of left upper extremity and left face. Developed fluctuating left-sided weakness. Neurological examination—left hemimotor-sensory syndrome with a left homonymous hemianopsia. Spinal fluid normal. Died of myocardial infarction.	Right temporal slow activity.	Right carotid angiogram—Sylvian fissure malformation.	Craniotomy—removal of malformation; anticonvulsants.
3	G.S. M	34 41	Recurrent tonic contraction of the fourth and fifth fingers of left hand. Developed generalization convulsions. Was noted to have position sense loss in fourth and fifth fingers of left hand.	Focal slowing in right inferior parietal region.	Pneumoencephalogram—shift of 3rd ventricle to left. After surgery, right carotid angiogram—right anterior parietal malformation from lateral surface to the falx.	Craniotomy—malformation seen. No excision attempted. Common carotid artery ligated; anticonvulsants.
4	S.S. M	Child 37 60	Febrile convulsions. Numbness in right upper extremity for 10-15 minutes, followed by shaking of right side, proceeding to generalized seizure. Neurological examination—right hemiparesis. Mild difficulty with speech. Monthly attacks of momentary "blankness."			Craniotomy—removal of small hematoma left inferior frontal region; hemangioma reported on pathology. Also, given radiotherapy. On anticonvulsants.

5	D.L. M	11 20 24	Shaking of left upper extremity, head and eyes turn to left. Occurred as often as 25 times a day. Had several admissions with no findings on x-ray, including angiography. Readmitted for uncontrollable seizures. Continues to have 5-6 seizures per day.	Diffuse slow activity with right temporal occipital focus.	Right carotid angiogram normal. Pneumoencephalogram normal.	Craniotomy for removal of irritable cerebral focus; was found to have a vascular malformation in superior frontal and posterior superior part of mid-frontal gyrus; anticonvulsants.
6	M.F. F	33 38	Seizure started with shaking of right upper extremity proceeding to generalized convulsion. Neurological examination—normal. Bruit heard, however, in head. Normal spinal fluid, except protein 182 mg%. Well.	Normal.	Left carotid angiogram—malformation close to midline fed by posterior branches of left middle cerebral artery and from right carotid circulation as well.	Anticonvulsants.
7	H.G. M	39 45 46 57	Episodic attacks of aphasia. Onset of grand mal seizures. Sudden severe left temporal headache, saw stars of various colors and was nauseated. Several weeks later, neurological examination—right Babinski sign. Spinal fluid normal. 2-3 severe headaches a year; 1-2 seizures a year.	Slow activity in temporal and occipital area, and diminished alpha on left side.	Left vertebral angiogram—large left parietal occipital malformation filling from posterior cerebral artery.	Anticonvulsants.
8	J.E. M	33 39	Twitching of right upper extremity, particularly shoulder, followed by weakness of that extremity; then developed grand mal seizures. Neurological examination normal, except for right hyperreflexia.	Right cerebral dysfunction.	Left carotid angiogram—vascular malformation frontoparietal junction fed by both anterior and middle cerebral arteries.	Anticonvulsants.

TABLE III—Continued

No.	Name, Sex	Age	Clinical History	EEG	X-Ray	Treatment
9	S.S. F	32	Attacks of shaking right hand, twitching of right face, and trouble speaking. Had had headaches in childhood on either side of head without nausea or vomiting.			
		35 37	Neurological investigation elsewhere. Seizures continued and she developed weakness of right upper extremity and right hemisensory syndrome. Spinal fluid normal.		Malformation demonstrated. Left carotid angiogram—malformation in left parietal area fed from anterior and middle cerebral arteries. Also visualized after right carotid angiogram.	Radiotherapy. Anticonvulsants.
		38	Killed in automobile accident.			
10	A.S. F	28	Episodes of feeling "woozy," had movements of right thumb and fingers and then automatic type activity. Spinal fluid normal.	Bitemporal bursts of slow waves, left more than right.	Pneumoencephalogram—normal. Left carotid angiogram—large collection of veins at junction of inferior sagittal sinus, straight sinus and vein of Galen.	Anticonvulsants.
		30	Has had one minor seizure.			
11	M.S. M	5	Left-sided seizures with concomitant deviation of eyes to left. Became more frequent with postictal weakness. Neurological examination—left hemiparesis and left homonymous hemianopsia. Spinal fluid normal.	Bilateral dysfunction increased in right parietal occipital area.	Pneumoencephalogram—normal. Right carotid angiogram normal.	Anticonvulsants.
		6	Seizures more frequent, speech became slow. Increased left-sided weakness.	Slow activity in parietal occipital region right more than left.	Right carotid angiogram—numerous fine vessels in right parietal area, also seen with brachial arteriogram and left carotid artery.	Anticonvulsants.
		7	Well.			
12	S.G. M	37	Focal seizures involving right lower extremity.			Craniotomy—angioma seen in left parietotemporal area.
		49	Hospitalized because seizures more frequent.			
		55	Head injury, hospitalized elsewhere. Xanthochromic spinal fluid.		Left carotid angiogram—malformation demonstrated in frontoparietal temporal area.	Radiotherapy. Anticonvulsants.
		57	Progressive right hemiparesis. Bruit heard on both sides of head.	Left-sided slow activity with temporal area accentuation.	Right carotid angiogram normal.	

13	E.W. F	Child 45	Since childhood, had vertex headaches preceded by blurring of vision, but not associated with nausea and vomiting. Twitching in left thumb and occasional entire left arm, with residual numbness in thumb. Six months later, developed severe left-sided headache, coma and left hemiparesis. Spinal fluid bloody. Bruit heard over right eye and both carotid arteries.		Right carotid angiogram—fronto-parietal malformation just to right of midline, fed by anterior cerebral artery and middle cerebral artery. Left carotid angiogram—malformation fed via anterior cerebral artery.	Anticonvulsants.
14	D.A. M	14 17 19	Episode of "colored lights" in front of both eyes, followed by headache with lights persisting. On occasion, he would then feel a squeezing sensation of his "stomach," his head turns to right and a generalized convulsion ensues. Family history of seizures. Hospitalized. Neurological examination normal. Spinal fluid normal. Seizures persist, but less frequent.	Right posterior-temporal delta and right temporal spikes.	Right carotid angiogram—temporal-occipital malformation filling from middle cerebral and posterior cerebral arteries.	Anticonvulsants.

TABLE IV
Group C. Patients Presenting with Generalized Seizures

No.	Name, Sex	Age	Clinical History	EEG	X-Ray	Treatment
1	E.G. M	42	Grand mal seizures. Neurological examination—normal. Spinal fluid normal.	Normal.	Right carotid angiogram—malformation of posterior portion of right temporal lobe near Sylvian fissure fed by middle cerebral artery.	Anticonvulsants.
		43	Well.			
2	E.H. F	21 41	Grand mal and psychomotor seizures. Five-week history of daily bifrontal headache lasting several hours. Neurological examination—organic mental syndrome. Spinal fluid normal.	Long runs and bursts of left temporal slow activity.	Plain skull x-rays calcification left temporal area. Left carotid angiogram—malformation deep left frontotemporal area from anterior clinoids to 2 inches posterior to clivus, also filling by right carotids and vertebral angiogram.	Anticonvulsants.
3	A.L. F	32 46	Grand mal seizures. Acute onset of headache and coma. Neurological examination—right hemiparesis. Spinal fluid bloody. Went rapidly downhill and died. Post mortem—subarachnoid hemorrhage due to vascular anomaly.		Left carotid angiogram—avascular mass left temporal region.	
4	R.L. F	17 23	Grand mal seizures. Normal neurological examination. 1-2 seizures per year.	Short bursts, slow activity, temporal area, left greater than right.	Pneumoencephalogram—normal. Right carotid angiogram—right frontoparietal malformation. No filling from left carotid artery.	Anticonvulsants.

5	K.D. F	2 6 7	<p>Transient loss of consciousness following head trauma. Two grand mal seizures occurred next day. Controlled by anticonvulsants.</p> <p>Began to have episodes in which her lips and eyes would move to the left.</p> <p>Tingling in gums sometimes associated with generalized convulsion, with weakness and numbness of left side postictus. Then developed almost continuous blinking and twitching of eyelids.</p>	Diffuse abnormality with slow activity left anterior temporal and spikes in right frontal area.	Right carotid angiogram—right posterior frontal parasagittal malformation fed by anterior cerebral artery. No filling from left carotid or vertebral arteries.	Anticonvulsants.
6	P.L. F	14 17	<p>Seizures—turning of head to right and then unconsciousness. Normal neurological examination. Spinal fluid normal.</p> <p>Seizures continue.</p>		Skull x-rays—sella turcica enlarged. Left carotid angiogram—Sylvian area malformation fed by middle cerebral as well as anterior cerebral arteries. Also filled from right carotid artery.	Anticonvulsants.

TABLE V
Group D. Patients Presenting with Other Neurological Signs and Symptoms

No.	Name, Sex	Age	Clinical History	EEG	X-Ray	Treatment
1	S.L. M	18	Inability to see on left side. Developed seizures postoperatively.			Craniotomy—right temporo-parietal occipital malformation seen. Not touched.
		26	Subarachnoid hemorrhage with residual left hemiplegia.			
		33	Progressive mental changes, left hemimotor-sensory syndrome with left homonymous hemianopsia and Babinski sign. Bruit heard over bone flap.	Slow activity in right frontotemporal region and left frontal region. Diminished alpha activity on right.	Right carotid angiogram—parietal-occipital malformation.	Right common carotid ligation, disappeared after ligation.
2	G.H. M	33	Headache and diminution of vision.			Craniotomy—angular left occipital lobe. Not touched. Then given radiotherapy.
		48	Headaches, organic mental syndrome; right homonymous hemianopsia. Bruit heard over left posterior part of head.	Diffuse slow activity, left more than right, occipital more than temporal. Diminished alpha in left occipital area.	Left carotid angiogram—malformation extending from parietal to occipital areas.	Left internal carotid and both posterior occipital arteries were clamped.
		49	Worsened mental changes. Right focal seizures progressing to generalized seizures. Patient died post-surgery.			
3	G.J. F	29	Weakness right leg and face, cleared after several weeks.			
		32	Severe headache and twitching right upper extremity. Right hemimotor-sensory syndrome. Patient died. Post mortem—left parietal intracerebral hematoma with vascular malformation.	Diffuse slow activity, left greater than right.	Pneumoencephalogram—mass in left hemisphere shifting to right of 3rd ventricle.	
4	S.M. M	32	Sudden onset severe frontal headache with residual right temporal field defect.			Anticonvulsants.
		41	Right-sided weakness, right homonymous inferior quadrantanopsia. Cerebrospinal fluid normal.	Normal.	Left carotid angiogram—vascular malformation extending from Sylvian groove to occipital pole. Filled also from callosomarginal branch of anterior cerebral artery.	
5	G.G. F	43	Doing well.			Craniotomy—excision of mass.
		36	Four-month history of occipital headache and humming noises on left side of head. Neurological examination normal, except occipital bruit heard. Cerebrospinal fluid was normal.		Left carotid angiogram—bifurcation along middle cerebral artery. Right carotid angiogram—communication via superficial temporal artery.	
		42	Doing well.			

izing in four, and normal or nonlocalizing in two. An intracranial bruit was heard in but one patient. Abnormal calcification on plain x-ray occurred in one case; another had an angioma of the occipital bone. Cerebral angiography demonstrated malformations of the temporal parietal area in three, and in the temporal occipital area in the three remaining. All these cases were treated symptomatically and the five available to follow-up are functioning well.

DISCUSSION

Six out of 65 cases of vascular malformation had "headache of vascular type" as an initial manifestation. In each case in which a malformation was demonstrated, it must be noted that there were other neurological symptoms or signs. During this same period, there were four additional cases of "headache of vascular type" in which arteriography was felt to be indicated and was performed. The headache was always on the same side in three of these cases; it was bifrontal in the fourth. Two of these had visual prodromata, one had sensory, another had atypical migraine or "sick headache." There were no findings on neurological examination. No vascular malformation was found in these patients. In 23 selected cases of 300 patients with the "migraine syndrome," similarly studied with arteriography, again no malformations were found (18).

In those patients with "headache of vascular type" who did have vascular malformations, the latter always involved the temporal or parietal occipital regions. It may be expected that posteriorly placed lesions involving the visual system would present with the visual symptoms of migraine. It is more difficult to understand when the headache was not that of classical migraine and had no visual or other prodromata. Indeed, the pathophysiology of the headache per se in these patients remains unclear.

In addition, posteriorly placed malformations seemed to correlate with the homonymous field defects found in three (§1, §2 and §4) of the patients in Group D, as well as patient §14 in Group B (D.A.), with visual phenomena and headache as an aura of a generalized seizure. However, there were many patients in whom the presence of malformation involving the temporal, parietal, occipital regions was not associated with either headache or visual signs or symptoms (Group A—§3, §7, §11, §14-19, §21-23, §26, §27, §30; Group B—§3, §6, §8-10, §12; Group C—§1-3, §6; Group D—§3). Visual phenomena may indeed appear to be unrelated at all to these areas. Among the patients initially presenting with subarachnoid bleeding (Group A), case §34 developed visual phenomena with episodes of intracerebral bleeding in the presence of a frontal pole malformation. Visual symptoms, albeit different, were precipitated during angiography as his vertebral basilar system was studied via subclavian artery catheterization.

Of the large number of patients one may see in clinical practice with the syndrome of "headaches of vascular type," very few indeed may be found to have their symptoms secondary to a vascular malformation in the posterior portion of the brain. In the 65 cases here described, there were but six cases

with "headaches of vascular type" as an initial symptom. In all these patients, there were other significant neurological symptoms and signs. Although these cases had posteriorly placed lesions, there were many other patients with similar findings on angiography without symptoms of vascular headache. It would appear that "vascular headaches" and posteriorly placed vascular malformations are not necessarily related. A patient with migraine alone would not appear to require investigation for a vascular malformation.

The survival time post initial hemorrhage cannot be stated definitively because of the relatively short follow-up in many of our cases. Follow-up data is available on twenty-three patients. Twelve are well in the first five years after hemorrhage. Nine are well five to ten years after bleeding. Two have had no subsequent hemorrhage twenty-four and thirty-one years after the initial episode. Twenty-five out of the total of forty patients had but one episode. Four patients died from the initial hemorrhage; four others had significant morbidity (defined as inability to care for self due to neurological involvement). Of those with subsequent hemorrhages, the interval between the initial episode and the one productive of significant morbidity or mortality was variable: three months, one year, two years, three years, eight years. Four patients died with the second episode; two additional ones had significant morbidity. Three patients went on to die following subsequent hemorrhages. Case #3 (Group A) survived thirty-four presumed episodes, many of which were documented, over a thirty-four year period without significant residua. At age 43, following her twenty-first episode, carotid ligation was performed. She continued to have episodes of intracranial bleeding and died at age 50, following her thirty-fifth episode.

Case #2 (Group A) had a twenty-four year interval between two hemorrhages and remains well six years after the last episode. Case #19 (Group A) has had at least seven episodes and remains well fourteen years post initial hemorrhage. Case #2 (Group E) has had eleven episodes over a thirty-year period and remains well.

Of a total of forty patients with subarachnoid hemorrhages, eleven (28%) died. Four additional cases, who remain alive, have significant morbidity. Thus, fifteen out of forty (37%) were dead or significantly disabled on short-term follow-up. An additional patient died during the postoperative period, following ligation of the carotid artery in an attempt to control frequent seizures. Total mortality or significant morbidity related to disease in our series is sixteen out of sixty-five patients (25%).

CONCLUSIONS

1. Cerebral vascular malformations may present as subarachnoid hemorrhage, focal seizures, or generalized seizures.

2. There does not seem to be any correlation between migraine headaches and vascular malformations of the brain. The patient with migraine alone does not appear to require investigation unless he develops other neurological signs or symptoms.

3. Vascular malformations which cause subarachnoid hemorrhage had an eventual mortality rate of eleven out of forty patients. Four additional patients had severe morbidity. Although patients may have repeated bleeding episodes without sequelae, the ultimate prognosis is guarded.

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Appendico-Vesical Fistula

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Intestinal vesical fistula is a recognized complication associated with such diseases as diverticulitis of the colon, regional enteritis, carcinoma and trauma. In the reported cases of intestinal vesical fistula, the colon is involved most frequently, with the ileum and appendix following in that order.

Kellogg (1) in a review of 592 cases of intestinal vesical fistula was able to identify the source of the fistula as follows: sigmoid colon 63%, rectum 16%, ileum 4% and appendix 4%. The appendix accounted for 27 cases (Table I). Higgins (2) reported a series of 382 cases of intestinal vesical fistulas and documented 13 cases (3.5%) as appendico-vesical fistulas. In a recent review of the literature, Fitzpatrick (3) compiled 49 cases of authenticated appendico-vesical fistulas and added two of his own.

CASE REPORT

L.C. (MSH #221704) was a 41 year old white, married, native-born television repairman admitted to The Mount Sinai Hospital on May 12, 1963, with a three-month history of intermittent, dull lower abdominal discomfort. Two months prior to this admission he had first noted a foul odor to his urine. He was admitted to another hospital where cystoscopy and cystogram study were reported to be within normal limits. Urine culture was positive for *E. coli*. A barium enema examination revealed the presence of barium and air in the urinary bladder but no fistulous communication could be identified. There was marked diverticulosis noted involving the left, the right and the distal transverse colon. He was treated with appropriate antibiotics and his symptoms cleared.

Within two weeks he had an exacerbation of symptoms and he was admitted to The Mount Sinai Hospital. Cystoscopy was repeated as was the cystogram but both failed to reveal any fistulous tract. Barium enema examination was performed and diverticulosis was again noted with the recto-sigmoid in spasm (Figs. 1, 2). A low-lying cecum was also reported and a short segment of the appendix was visualized. No definite communication with the urinary bladder could be demonstrated although barium and air were visualized in the urinary bladder on two barium enema examinations (Figs. 1, 2).

The patient's past history failed to uncover any preceding signs or symptoms compatible with an attack of acute pelvic appendicitis.

Physical examination revealed a mildly obese white male in no acute distress. Vital signs were: blood pressure 140/80, pulse 80, respirations 16, temperature 99.0°. The entire physical examination was within normal limits. Rectal examination and sigmoidoscopy to 25 cm were normal.

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Laboratory examination included: hemoglobin 15.4 Gm, WBC 7,900 with a normal differential count, urinalysis normal, BUN 14 mg%, FBS 98 mg%, alkaline phosphatase 8.8 mg%.

The patient underwent surgery for an intestinal vesical fistula on May 16,

TABLE I
Documented Cases of Appendico-Vesical Fistula

Authors	Reported Cases
Kellogg (1)	27
Higgins (2)	13
Pemberton, Pool and Miller (4)	5
Hyman and Capos (5)	3
Fitzpatrick (3)	2
Parton (6)	1
	51 cases



FIG. 1. Air visualized in urinary bladder on barium enema examination.

1963. The abdomen was entered via a left rectus muscle retracting incision. A mass was noted in the pelvis which incorporated the sigmoid colon, the dome of the bladder and the cecum. There was marked diverticulosis of the sigmoid and descending colon with much less involvement of ascending colon and the distal transverse colon. The sigmoid colon was dissected free from its lateral

peritoneal attachment and traced to the mass. The sigmoid was dissected free from the mass and it was apparent that there was no communication to the urinary bladder from the sigmoid colon. The cecum was then mobilized and on tracing it down to the mass it was noted that it was intimately attached to the superior-lateral portion of the bladder wall. The base of the appendix was identified and dissected free for 2 cm but the remaining portion of the appendix

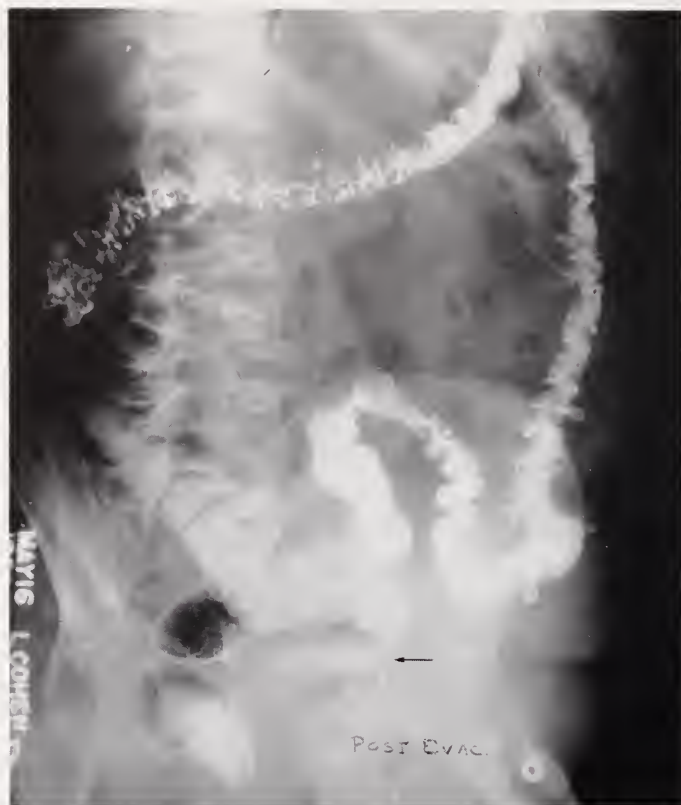


FIG. 2. Air and barium visualized in urinary bladder on post-evacuation barium enema examination. Note low-lying position of cecum.

was seen to be deeply imbedded in the wall of the bladder. The appendix was transected at its base after the appendiceal vessels had been clamped, divided and ligated. It was decided to leave the remainder of the appendix *in situ* rather than perform a partial cystectomy. There was no evidence of infection or abscess formation. Drains were placed to the pelvis and brought through the lower portion of the wound. The abdomen was closed with interrupted figure-of-eight $\#30$ stainless steel wire sutures, and the skin approximated with interrupted silk sutures.

The patient's postoperative course was uneventful and he was discharged

home on the eighth postoperative day. He has resumed his normal full activities and has had no further symptoms thirteen months following operation.

DISCUSSION

The mortality rate for acute appendicitis has steadily decreased in recent years. In 1955, approximately 5,000 deaths from acute appendicitis were recorded in the United States, a mortality rate of 1.4 per 100,000 population (7). In 1961, recorded deaths from acute appendicitis decreased to 1819 cases, a mortality rate of 1.0 per 100,000 population (8). The complications of perforation and peritonitis accounted for most of the deaths in cases of acute appendicitis, whereas cases without perforation were associated with practically no mortality (9).

The well-described type of appendicitis presenting with generalized abdominal pain later localizing to the right lower quadrant associated with nausea, vomiting, anorexia and low grade fever is usually diagnosed early in the course of the illness. However, the acute pelvic type of appendicitis may go undiagnosed unless tenderness is elicited in the pelvis on rectal examination. Concomitant onset of diarrhea should raise the index of suspicion for acute pelvic appendicitis. It is this type of appendicitis which undetected may go on to appendico-vesical fistula. Should perforation ensue and abscess formation develop, it is not uncommon, particularly in the male, for the urinary bladder to form a part of the abscess wall. Thus, appendico-vesical fistula results by the adherence of the distal portion of the appendix to the bladder wall, and the formation of the ensuing inflammatory process. As noted in Table I, this complication of perforated appendicitis is quite rare having only been recorded in 51 previous cases (3).

Perforation into the urinary bladder is dependent on a combination of anatomical variables: 1) low-lying cecum, 2) a relatively long appendix, 3) adherence of the tip of the appendix to the wall of the bladder, 4) perforation of the appendix, 5) abscess formation with bladder wall comprising portion of abscess formation, 6) continued inflammation.

Symptoms of appendico-vesical fistula fall into two categories: 1) gastrointestinal symptoms simulate those of an acute pelvic appendicitis and may develop into bizarre, vague, lower abdominal pains and later bowel habit changes if surgery is not performed. It is possible that intestinal obstruction may ensue if loops of small bowel become markedly involved; 2) genito-urinary symptoms may vary from mild complaints of frequency to those of marked cystitis complicated by pneumaturia, fecaluria, hematuria, and signs of ascending urinary infection. It is not unusual for the urologist to discover the intestinal-vesical fistula.

Many of these patients may go unrecognized for long intervals. Mayo (10) noted an average of 18.5 months of symptoms in 48 cases prior to diagnosis. Hyman (5) had one patient with a two and one-half year history of symptoms and another patient with a preceding history of eight months.

The predominance of intestinal-vesical fistulas in the male patient is approximately three times that in the female patient. This is usually explained by noting the anatomical interposition of the uterus between the bladder and the rectum in the female. Parton (6) was able to verify the sex of the patient in 23 cases of appendico-vesical fistula and noted that 19 (83%) were male.

In the diagnosis of an intestinal-vesical fistula, barium enema, cystoscopy with cystogram, and the use of a contrast medium such as indigo carmine are most helpful. The barium enema may reveal the fistulous tract. However, a negative examination does not rule out such a tract. The fistulous tract may be of a ball-valve type and allow both barium and air to enter (Figs. 1, 2) without outlining the communication. Four barium enemas were performed on the reported patient. All revealed barium and air in the urinary bladder, but none revealed any fistulous tract. The use of cineradiography techniques may yet prove helpful in outlining such a communication in future cases.

Cystoscopy may furnish a clue to the area of fistulization by noting the region of mucosal injection and edema. However, it is not a simple task to localize this region when there is generalized infection, marked edema and inflammatory changes in the bladder. The cystogram may assist in establishing the diagnosis should it reveal the site of external pressure, or should the dye outline the fistula. Similarly, recovery in the stool of indigo carmine instilled in the bladder may confirm the diagnosis of intestinal-vesical fistula.

SUMMARY

Appendico-vesical fistula is a rare type of intestinal-vesical fistula with only 51 previously reported cases. Approximately 4% of intestinal-vesical fistulas arise from the appendix. The usual pathogenesis of such an appendico-vesical fistula is unrecognized acute pelvic appendicitis which goes on to perforation, abscess formation, continued inflammation and ensuing perforation into the urinary bladder. Anatomically, a low-lying cecum, relatively long appendix, adherence of appendiceal tip to bladder wall and abscess formation incorporating part of bladder wall favor this complication.

Mortality rate for acute appendicitis has fallen from almost 5,000 deaths in the United States in 1955 to 1819 deaths in 1961, a rate of 1.0 per 100,000 population. It is evident that most of these deaths were from complications of perforation and peritonitis.

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Carl Koller and Cocaine

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The adaptation of the local anesthetic properties of cocaine to surgical procedures upon the eye was the epoch-making discovery of Dr. Carl Koller in 1884. Very recently his daughter, Hortense Koller Becker has written and had published in the *Psychoanalytic Quarterly** a vivid portrayal of the life of her father in Austria during his younger years and the social and professional and academic surroundings in which the great achievement was accomplished. It is a beautifully written manuscript composed with the accuracy and the devotion of a loving daughter, and based upon a mass of voluminous letters carefully preserved and found only after his decease.

In his later life Carl Koller served for many years as Attending Ophthalmologist at Mount Sinai Hospital. To those of us who remember his vivid personality the discovery in his youth of the local topical use of cocaine constitutes a fascinating story.

Koller was born in Schuttenhofen, then Austria, on December 3rd, 1857, and was educated in medicine at the University of Vienna. His lifetime encompassed most of the great discoveries of medicine, asepsis, anesthesia, vaccines, antibiotics and advanced surgical facilities. At the age of nineteen he was matriculated as a student of medicine at the University of Vienna with the facilities of the renowned Allgemeine Krankenhaus for the study of the clinical material. Very early he demonstrated his acquisitive faculty toward original thought and research publishing an extensive study on the development of the embryological mesoderm in man and animals. Throughout his early life in Vienna he was closely associated with Sigmund Freud as a personal friend with whom he worked and thought and corresponded throughout these years.

Freud was much interested in the pharmacological effects of the coca leaf obtained from the coca plants grown in Peru and used by the Indians in the high plateaus of the Andes for its stimulatory effect when chewed, overcoming fatigue. Freud had tried the use of the leaf drug as a substitute for morphine in an addict suffering from trigeminal neuralgia. The general effects of the coca leaf, and of cocaine (separated as an alkaloid in 1856) were well known. The local numbing effects of cocaine on the lips and tongue had been noted and also dilatation of the pupils of the eye (Von Anref). Freud urged Koller to experiment with cocaine, to take it by mouth and observe the effects generally and locally. But, Koller who had always shown a preference for ophthalmology, conceived the idea of studying the effects of cocaine on the eye. Instilling a drop of cocaine solution into the eye of a frog, Koller noted that all sensibility in the eye was lost, the cornea could be rubbed and gently abraded

* Hortense Koller Becker: *The Psychoanalytic Quarterly*, 32: 309, 1963.

without eliciting the winking reflex. Much startled, he instilled the solution into his own eye and that of a fellow worker corroborating the finding that complete anesthesia was thus attained even against rubbing cotton fibers over the eye surface and even indenting the cornea.

The first paper on the use of cocaine on the eye was read at the Heidelberg Ophthalmological Society on September 15th, 1884, the paper actually being read in absentia by his associate, Dr. Josef Brettaner of Trieste. The remarkable discovery was rapidly disseminated through the scientific world, hailed and accepted immediately as a great boon to humanity. From all over the world letters poured in and the extension of the use of cocaine to the nose, pharynx, and larynx was soon adopted. Koller's fame abroad and in the United States was widespread.

In spite of his world-wide scientific accreditation Koller had in Vienna many enemies as well as friends. "He was not only a Jew (in itself a drawback to promotion in the University) but a difficult tempestuous young man, one who never could be compelled to speak diplomatically even for his own good."

He had served his compulsory military training in the Austrian Army in 1876 as an Oberarzt in the Army Reserve. One day (1885) at the General Hospital a patient was brought in by stretcher with a bandaged injured finger. The young Koller perceiving the bandage to be constricting the digital circulation attempted to loosen the bandage when one of Billroth's assistants hurled at him an insult that sounded like "Impudent Jew." A resounding box on the ear was the immediate reflex answer. A duel with sabers was arranged as a necessary sequel. Sharp, thin light blades were chosen; no bandages to be used, and the right to continue until one or the other party was unable to defend himself. On the third round of thrusts Koller wounded his opponent on his head and right arm, sufficiently severely to terminate the duel; honor was appeased. Koller had never had the slightest experience in dueling, had time to take only one hasty lesson; one of his seconds was Dr. Sigmund Lustgarten (in later life Attending Dermatologist at The Mount Sinai Hospital in this city).

Anti-Semitism was particularly rife in Austria at this time, and Koller soon realized that now all hope of advancement was more or less nullified. He left for Utrecht, Holland, on the suggestion of his close friend Freud, later immigrating to London in the hopes of achieving an appointment in ophthalmology, again with disappointment; in 1888 he came to America and lived in the U.S.A. for fifty-six years until his death in 1944 at the age of eighty-seven years.

In 1901 he was appointed Adjunct Attending Ophthalmologist and Aural Surgeon at Mount Sinai serving under the renowned Dr. Emil Gruening (father of the present Senator from Alaska); from 1909 to 1920 he was Attending Ophthalmologist at this Hospital.

Honors, many honors, well deserved, came to this extremely modest man later in his life; in 1922 the Howe Medal of the American Ophthalmological

Association; the Kussmaul Medal of the Heidelberg Medical Faculty (1929); Medal of Honor of the New York Academy of Medicine (1930); the Medal of Honor of the American Academy of Ophthalmology and Otology (1934).[†]

Personal Note: As an intern in 1908 and 1909 I had the honor to serve under Koller in the Department of Ophthalmology at Mount Sinai Hospital, and also under Sigmund Lustgarten in the Department of Dermatology. Koller was an upright man of extreme intelligence with a broad scientific interest. He was direct, always outspoken, frank, often critical, always just and always kindly. He was a competent surgeon who brooked no false ideas and who quickly recognised fallacious reasoning or pseudoscientific quibbles. His humour was delightful, he was often whimsical and impatient, at times ironic and sardonic. He was a true, cultured gentleman, reliable, fearless, direct. He despised insincerity in medical practice. He lived to old age, with wide interests in physics, geography, mountain climbing, astronomy, polar expeditions, history and travel.

The Mount Sinai Hospital was thus twice the benefactor of the anti-Semitism of Austria of the last century, being ennobled by the presence of two such great scholars as Koller and Lustgarten. Sad that this country did not also have the honor of receiving into its presence Sigmund Freud himself.

[†] Obituary of Carl Koller, by Percy Friedenber, J. of the Mt. Sinai Hosp., 11: 308, 1945.

A CLINICAL NOTE

USE OF THE INTRAVENOUS CATHETER FOR PERICARDIOCENTESIS AND THORACENTESIS

PAUL A. KIRSCHNER, M.D., AND B. GEORGE WISOFF, M.D.

New York, N. Y.

Percutaneous introduction of plastic catheters into blood vessels, body cavities, heart chambers, subarachnoid space and other areas has received widespread approval. The ubiquitous sterile intravenous catheter unit* has already been adapted to the aspiration of ascitic fluid and pneumothorax.

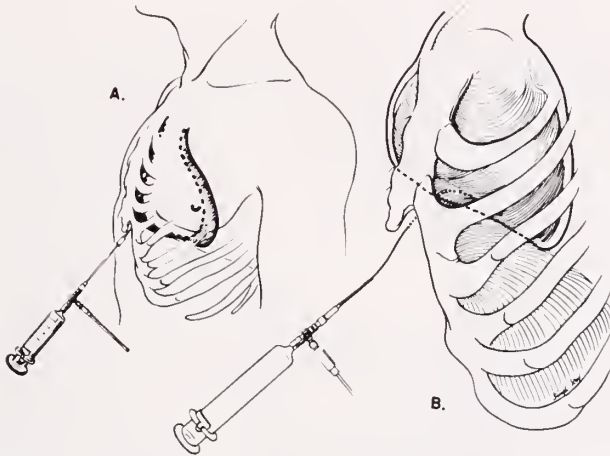


FIG. 1A. Subxiphoid percutaneous pericardial puncture with needle (catheter within needle).

FIG. 1B. Catheter has been advanced into pericardial cavity. Needle has been withdrawn. Note flexibility of catheter as it rests adjacent to myocardium.

However, pleural and pericardial effusions are usually "tapped" using rigid needles. The dangers of lacerating the underlying lung or heart, the necessity for prolonged immobility of the patient and the physician, and the relatively fixed position of the needle point in the cavity are well known.

Introduction of a plastic catheter through a needle, subsequently withdrawing the needle and attaching the hub of the catheter to a three-way stopcock obviates the above mentioned difficulties. The flexible catheter cannot damage the lung or the heart; it can be advanced or withdrawn for more thorough aspiration of fluid; and it can be fixed *in situ* for prolonged or intermittent aspiration. The patient and physician are granted more mobility and comfort.

From the Division of Cardio-thoracic Surgery, Department of Surgery, The Mount Sinai Hospital, New York, N. Y.

* Venocath (R) (Abbott). Intracath (R) (C. H. Bard).

These advantages have manifested themselves in the clinical practice of The Mount Sinai Hospital during the past eighteen months. No contraindications have been observed.

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Radiological Notes

CLAUDE BLOCH, M.D., AND HARVEY M. PECK, M.D.

New York, N. Y.

CASE NO. 240

SUBMITTED BY PHILIP LEVIN, M.D.

This 50 year old, right-hand male was admitted to The Mount Sinai Hospital in 1961 because of a progressive left visual field defect of seven months' duration.



Case 240, Fig. 1A. Anterior-posterior projection of carotid angiogram. Arrow indicates the Artery of Bernasconi and Cassinari (tentorial meningeal artery). It apparently originates from the intracavernous portion of the internal carotid artery. With an undulating course it winds medially and upward.

From the Department of Radiology, The Mount Sinai Hospital, New York, N. Y.

In December 1956 a right parietal meningioma was removed. In August 1957 a generalized convulsion occurred. Left-sided weakness became pronounced. A right carotid angiogram revealed a right fronto-parasagittal mass; an encapsulated falx meningioma was removed from its dural attachment.



Case 240, Fig. 1B. Lateral projection of carotid angiogram. Arrow indicates the Artery of Bernasconi and Cassinari (tentorial meningeal artery). Note its apparent origin from the intracavernous portion of the internal carotid artery. It courses along the lower border of the falx and angulates upward at the edge of the tentorium. In addition there is a large, posterior branch of the middle meningeal artery which courses to the posterior parietal area.

In February 1961 slight left visual field defect and mild right-sided pressure headaches were noted. Twitching of the left foot occurred.

A right carotid angiogram (Figs. 1A, 1B) revealed the Artery of Bernasconi and Cassinari. It apparently originated from the intracavernous portion of the internal carotid artery and ran along the lower border of the falx, angulating upward at the edge of the tentorium. On the anterior-posterior projection the vessel coursed medially and upward. The pneumoencephalogram demonstrated the right atrium and occipital horn to be displaced anteriorly.

The patient underwent craniotomy and a right occipital meningioma weighing 72 grams was removed. The postoperative course was unremarkable. When last seen the patient was well and the neurological examination was normal except for the left visual field defect.

CASE NO. 241

SUBMITTED BY PHILIP LEVIN, M.D.

This 43 year old female entered The Mount Sinai Hospital for the second time in 1959 because of left hemiparesis and gait difficulty of one year's duration.

The patient had complained of headaches upon awakening since the age of 15. In 1948 she suffered seizures when five months pregnant. She was admitted in 1956 at which time left hemiparesis, left hemisensory defect, and left-sided hyperreflexia with a left Babinski response were noted. A right temporal-parietal craniotomy was carried out and a bilobed meningioma, each lobe the size of a walnut, was removed. In addition, a fairly large meningioma *en plaque* was removed from the parietal parasagittal area. Several smaller meningiomas were removed with a curet; their dural bases were cauterized. Following operation there was some improvement in the strength of the left lower extremity and, on discharge, the patient was able to walk with a cane.

The patient was readmitted in 1959 with a history of increasing left-sided weakness. Urinary incontinence and memory deficit had occurred.

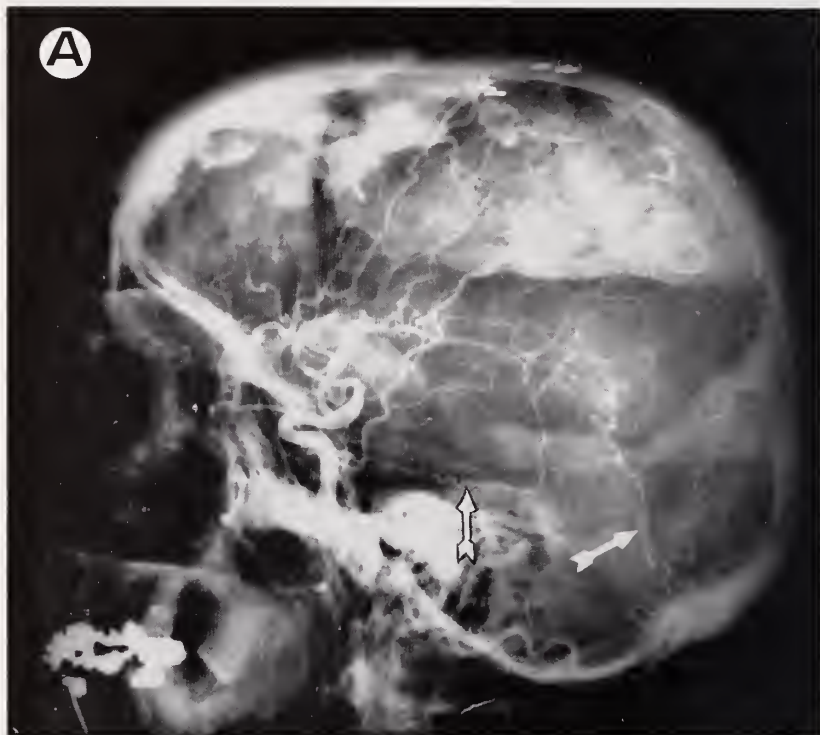
The left carotid angiogram was remarkable in the visualization of three meningeal arteries (Figs. 1A, 1B). The middle meningeal artery, the Artery of Bernasconi and Cassinari (tentorial meningeal artery), and the posterior meningeal artery arising from the occipital artery were prominent. The Artery of Bernasconi and Cassinari presented the characteristic tightly coiled appearance and, on the lateral film, appeared to arise from the intracavernous portion of the internal carotid artery. It ran directly backward for a distance of 5 centimeters and then turned sharply upward to end in a group of thin, separated vessels. In the anterior-posterior projection the vessel coursed medially and upward.

A right fronto-parietal craniotomy was carried out. An anterior parietal parasagittal meningioma the size of a lemon was removed. A separate daughter tumor was removed from the right side of the falx. The patient made a slow recovery and was able to ambulate with a cane on discharge.

DISCUSSION OF CASES NO. 240 AND 241

The Artery of Bernasconi and Cassinari (tentorial meningeal artery) is significant because it may indicate the presence of a meningioma. While originally thought to be diagnostic of tentorial meningiomas (1), it has occurred in anterior parasagittal, falx, and occipital meningiomas. It has also been noted in cases of arteriovenous malformations and has appeared, as an incidental finding, in other conditions.

The tentorial meningeal artery presents a coiled appearance. It apparently arises from the intracavernous portion of the internal carotid artery and, in the lateral view, courses backward and then upward in the region of the tentorium. In the anterior-posterior projection it proceeds, with an undulating course, upward and medially to the midline. Its origin is below that of the anterior choroidal and posterior cerebral arteries. Also to be differentiated is the primitive trigeminal artery. This proceeds directly to the basilar artery; it



Case 241, Fig. 1A. Lateral projection of carotid angiogram. Arrow indicates the Artery of Bernasconi and Cassinari (tentorial meningeal artery). The second arrow (right) points to the posterior meningeal artery which originates from the occipital artery. Both arteries end in a group of thin, separated vessels. The middle meningeal artery is also visualized. Diffuse hyperostosis of the cranial vault is present.

is considerably larger in caliber. A posterior branch of the middle meningeal artery can be distinguished by means of the anterior-posterior projection.

This artery was originally considered by Bernasconi and Cassinari to be part of the external carotid tree (1). However, Frugoni, Nori, Galligioni, and Giammusso found the artery to be present in a case where injection of the internal carotid artery alone was performed (2). In a subsequent external carotid artery injection the artery was not found. This supports its origin from the internal carotid artery.

Meningiomas draw their blood supply from internal and external carotid sources. As the tumors enlarge the supplying vessels provide more blood.

Small vessels hitherto unnoticeable may become visible angiographically. Tentorial meningeal arteries are not mentioned in standard textbooks of anatomy. Stattin reports the only anatomical work done on this topic (3). Twenty cadavers were examined after injection of a water-soluble dye into the internal carotid artery. Using a special microdissection technique, a very narrow vessel was found arising from the carotid siphon in three cases. This vessel arose from the siphon in the region where the internal carotid artery enters the cavernous sinus and passed backward to ramify in the anterior part of the tentorium.

The Artery of Bernasconi and Cassinari has been recorded thirty-one times



Case 241, Fig. 1B. Anterior-posterior projection of carotid angiogram. Arrow indicates the Artery of Bernasconi and Cassinari (tentorial meningeal artery). It courses medially and upward.

previously in the literature. Bernasconi and Cassinari reported it to be present in five cases of tentorial meningioma (1). Frugoni, Nori, Galligioni, and Giammusso reported it in eight cases of tentorial meningiomas, two cases of meningioma of the posterior third of the falx, and one case of anterior parasagittal meningioma (2). Wickbom and Stattin reported eight cases of tentorial meningioma and two cases of vascular malformation in which this artery was present (3, 4). It was also present in five other cases as an incidental finding. These cases included thrombosis of the middle cerebral artery, berry aneurysm of the middle cerebral artery, carotid stenosis, subarachnoid hemorrhage, and intracranial bruit.

Case Report: THE ARTERY OF BERNASCONI AND CASSINARI (TENTORIAL ME-

NINGEAL ARTERY) IN CASES OF INTRACRANIAL MENINGIOMA. PRESENTATION OF TWO CASES.

ACKNOWLEDGMENT

These cases are presented through the courtesy of Dr. Sidney W. Gross.

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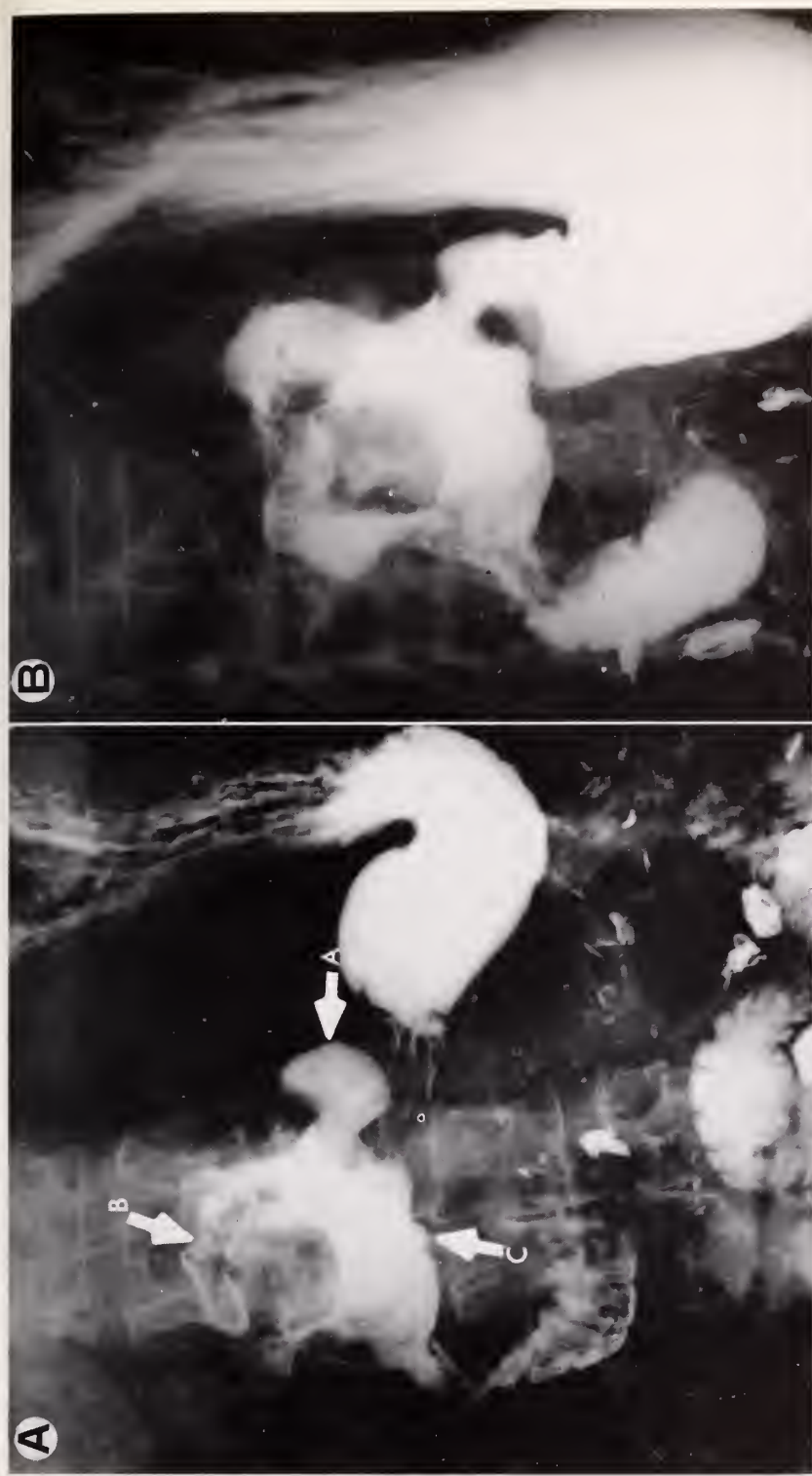
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CASE NO. 242

This 70 year old female was admitted to the hospital because of progressively severe epigastric pain radiating to the back, weakness and weight loss. The first symptoms occurred approximately two years before admission. There was no nausea nor vomiting and the epigastric pain was not related to fatty foods. There was no history of jaundice. There was a total weight loss of 70 lbs. in two years.

Physical examination revealed normal vital signs. There was no evidence of icterus. Positive findings were limited to the abdomen where an ill-defined, orange-sized, firm, slightly tender mass was palpable in the epigastrium. The liver edge was felt two fingerbreadths below the costal margin and was hard and nontender. Laboratory examination revealed a hemoglobin of 6.6 Gm, normal white cell and differential count. Prothrombin time was normal. Bilirubin was also normal. Total protein was 5.67 Gm%, with an A/G ratio of 2.22/3.43. Cephalin flocculation was negative. Guaiac stools were 4+. Urinalysis showed 4+ bile. Radiographic examination of the abdomen in the supine projection revealed a ringlike calcific density in the right upper quadrant 3 cm in diameter. Just medial and inferior to this calcification, there was a diamond-shaped structure, 5 × 6 cm in diameter, outlined by air with scalloped superior and lateral contours. No soft tissue masses were noted. Barium meal examination revealed no abnormalities of the esophagus or stomach. The pyloric channel was also normal. The base of the duodenal bulb was identified and was normal in contour and size. One centimeter beyond the base of the duodenal bulb, there was a large collection of barium occupying the entire distal portion of the first part of the duodenum. The contours of this structure were scalloped and the quality of the barium within it was amorphous (Fig. 1). Within this enlarged and distorted first portion of the duodenum, there was a smoothly demarcated, sharp filling defect measuring 1.5 cm in diameter. The duodenal sweep and ligament of Trietz appeared normal. There was no air or barium in the hepatic region suggestive of biliary ducts.

During the course of the patient's hospitalization there was intermittent



Case 242, Fig. 1A. Roentgenogram in the postero-anterior projection reveals a normal stomach and pylorus. The base of the duodenal bulb (A) is normal in size and not unusual. Just distal to the base there is a large 4 x 5 cm barium-filled structure (C) with scalloped contours and containing amorphous barium. Within this structure, there is a sharply delineated, 1.5 cm in diameter, round filling defect (B).

Case 242, Fig. 1B. The same structures are visualized in the right anterior oblique projection.

fever ranging up to 102°. She received several blood transfusions and laparotomy was performed. At operation, a large bulky neoplasm was noted to involve most of the fundus of the gallbladder with infiltration into the first portion of the duodenum. As a result of the invasion of the duodenum, a large cholecysto-duodenal fistula with a periduodenal abscess was found. A biliary calculus, 1.5 cm in diameter, was noted to lie within this fistulous tract. Common duct exploration was not performed because of the large amount of tumor obscuring the biliary ducts. The duodenum and the abscess were resected and an end-to-end anastomosis of the proximal portion of the stomach and the distal duodenum were performed. Histological examination revealed infiltrating squamous cell carcinoma of the gallbladder.

DISCUSSION

The roentgen findings on gastrointestinal series produced by carcinoma of the gallbladder have recently been extensively reviewed by Khilmani *et al.* (1). The changes are usually subtle and limited to the post bulbar region of the "superior flexure" of the duodenum. When the tumor invades the wall of the duodenum, it may cause an ulceration of the first part of the duodenum. When this destruction becomes extensive a cholecysto-duodenal fistula may ensue. Carcinomatous cholecysto-duodenal fistulae represent only about 2 per cent of all the spontaneous internal fistulae between the gallbladder and the upper gastrointestinal tract. Over 90 per cent are due to cholelithiasis and about 5 per cent are on a basis of a perforating duodenal ulcer (2). The present case is unusual because of the extent of the destruction of the "duodenal knee" with the formation of a large periduodenal abscess. The filling defect noted within the large duodenal bulb gives it a bizarre appearance but the sharpness of this defect suggests the presence of a stone. This calculus was noted to contain a rim of calcium on the plain film of the abdomen. This case is unusual clinically in that although this was a squamous cell carcinoma of the gallbladder and therefore probably on the basis of metaplasia secondary to chronic cholecystitis and cholelithiasis, there was never any history of jaundice. In the differential diagnosis of a massively enlarged duodenal bulb with irregular contours, the most likely possibility is lymphosarcomatous involvement of the duodenum. Usually in this disease there is evidence of disease on both sides of the pylorus but occasionally the only roentgen manifestation is that of a markedly dilated duodenal bulb with nodular scalloped contours. A giant benign ulcer of the duodenal bulb can also present as a large bulb with unchanging contours. In this disease, however, the borders of the ulcerated duodenal bulb are not as scalloped and irregular and there is a considerable amount of surrounding spasm and irritability.

On very rare occasions, a large perforation of a duodenal ulcer can mimic a massively enlarged and distorted post bulbar region. Often lucent filling defects within the barium filled duodenum represent retained food particles.

Case Report: SQUAMOUS CARCINOMA OF THE GALLBLADDER WITH CHOLECYSTO-DUODENAL FISTULA.

ACKNOWLEDGMENT

The editors wish to thank Drs. S. Daniel Blum and Sidney Cohen of the Booth Memorial Hospital, Flushing, N. Y., for permission to present this case.

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CASE NO. 243

A 70 year old senile female, resident in a nursing home, was referred for a gastrointestinal radiologic examination because of anemia and a palpable abdominal mass.



Case 243, Fig. 1. Supine view of the abdomen during gastrointestinal series shows a grapefruit-sized mass with a very large central excavation measuring 15 cm in greatest diameter. The lesion is in the first loop of jejunum distal to the ligament of Treitz. The mass displaces surrounding loops of bowel, the fourth portion of the duodenum, and the stomach.

The available history is fragmentary. Rectal bleeding had occurred approximately three months previously at which time a gastrointestinal series was performed at another institution. A duodenal ulcer was reported and the patient was treated with blood transfusions and conventional medical regimen. Because of her mental status she was transferred to a nursing home where weakness and anemia were again noted.



Case 243, Fig. 2. Following two weeks of radiotherapy with a tumor dose of approximately 1400 rads, repeat study shows the excavation to measure 5 cm in greatest diameter. Note the nodular contour within the excavation.

Appropriate investigation was advised but was refused by the family. Blood transfusions were again given but anemia persisted and a mass became palpable in the left mid-abdomen. Consent for investigation was finally obtained and the patient was referred for radiographic studies.

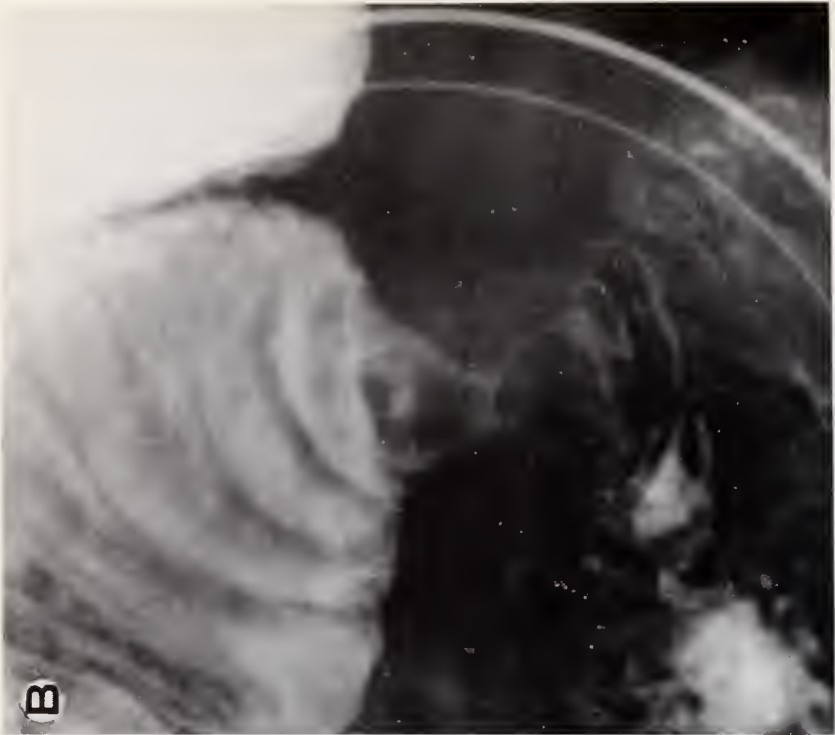
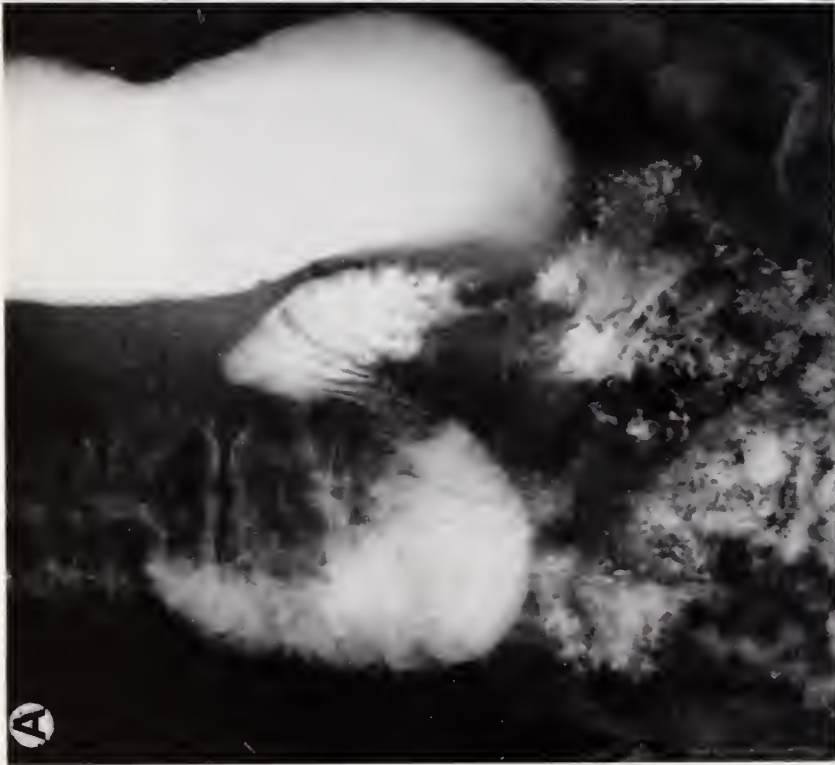
Barium enema revealed extrinsic pressure on the distal transverse colon by a mass; a peculiar angular collection of air was present within the mass suggesting an ulcerating neoplasm. Gastrointestinal series demonstrated a very

large irregular excavation measuring 15 cm in greatest diameter which was located in the course of the first loop of jejunum distal to the ligament of Treitz (Fig. 1). The involved segment was surrounded by a grapefruit-sized mass which displaced the surrounding loops of small bowel, the fourth position of the duodenum, the stomach, and the transverse colon. Malignant lymphoma was suggested as the most likely diagnosis.



Case 243, Fig. 3. Following five weeks of radiotherapy with a tumor dose of approximately 3500 rads, a third study shows the excavation to measure 3.5 cm.

A course of orthovoltage radiation therapy was instituted using two opposing 10×15 cm portals. Repeat radiographic examination was performed two weeks later by which time a tumor dose of approximately 1400 rads had been delivered (Fig. 2). A marked reduction in the size of the excavation was noted which now measured 5 cm in greatest diameter; the mass was proportionately smaller as well. At the conclusion of a five-week course of therapy, a tumor dose of approximately 3500 rads had been delivered. A third radio-



Case 243, Fig. 4A. Six weeks following the completion of radiotherapy, a final examination shows no discrete ulcer and no apparent mass. A short strictured segment is present instead and there is moderate retention of barium proximal to the stricture and moderate dilatation of the stomach and duodenum.

Case 243, Fig. 4B. Spot radiograph of the strictured segment demonstrates smooth margins, but no ulceration, nodularity or mass.

graphic study showed further reduction in the size of the excavation which now measured 3.5 cm (Fig. 3). A final study was performed six weeks after completion of radiotherapy (Fig. 4, A and B). In place of the original lesion, there was noted a short stricture with smooth margins, but no ulceration, nodularity or mass. There was moderate retention of barium proximal to the stricture and moderate dilatation of the stomach and duodenum.

Clinically, the abdominal mass was no longer palpable. The anemia responded completely and no further blood transfusions were necessary. The patient ate well, gained weight, and there were no signs of bowel obstruction despite the final radiographic findings.

Six months later the patient developed multiple subcutaneous nodules; one of these on the chest wall was biopsied. The pathologist reported malignant lymphoma, reticulum cell sarcoma type. The patient subsequently deteriorated rapidly and died. Post mortem examination was refused.

DISCUSSION

Although radiation therapy in general is the treatment of choice for malignant lymphomatous disease, surgery often plays an important role in cases of primary involvement of the bowel. In many cases, the desire to establish a histologic diagnosis dictates initial surgical intervention. It is sometimes forgotten that a short course of radiotherapy can lead to a firm clinical diagnosis on the basis of rapid tumor shrinkage; if the initial effect is favorable, the course of therapy can then be appropriately extended for definitive treatment.

Case No. 243 is presented because it affords an unusually clear documentation of the response of reticulum cell sarcoma to radiation. Not only is it worth while to note the disappearance of the enormous excavating neoplasm, but the end result of a smooth short stricture is of distinct interest.

Case Report: PRIMARY RETICULUM CELL SARCOMA OF THE JEJUNUM WITH RESPONSE TO RADIOTHERAPY.

ACKNOWLEDGMENT

The editors wish to thank Dr. J. Neiman, Good Samaritan Hospital, Suffern, N. Y., for permission to present this case.



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Diseases Associated with Some Enzymic Defects in the Gonads and Adrenal Cortex

A Classification Based on a Theory of the Biogenesis of the Feminizing and Virilizing Syndromes

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It is now commonly accepted that in congenital adrenocortical hyperplasia there is an enzymic defect usually involving 21-hydroxylation but at times involving other enzymes (1, 2, 27). It has also been shown that androstenedione and testosterone can be converted into estrogen by the adrenal cortex (4) as well as by the ovary (5) and testis (4) and therefore may act as intermediaries in the biosynthesis of estrogen (3-7, 29, 30, 41, 42) (Fig. 1). Only recently, however, has the elaboration of testosterone by these organs been unequivocally demonstrated (8-10) although the formation of androstenedione (7, 42, 43) in these tissues had previously been known. It would therefore seem possible that disorders might arise as a result of either the increased or decreased conversion of androstenedione and testosterone into estrogen in the adrenal cortex or gonads. On the basis of such a concept, many of the known disorders of the adrenal and gonads are readily explained and understood.

The ratio of conversion of androgen into estrogen, particularly in the gonad, is probably in large measure controlled by the genetic sex pattern and for this reason, the conversion of androgen to estrogen is minimal in the male and maximal in the female under normal circumstances.

There is also evidence that the conversion of androgen to estrogen may be in part regulated by luteinizing hormone (16) or at least that estrogen secretion is increased by this pituitary or chorionic fraction. This evidence includes the increased urinary excretion of neutral 17-ketosteroids [2×] and estrogens [5-16×] in men given chorionic gonadotropin (35, 38, 43) and the *in vitro* demonstration by the Hollanders of the facilitation of this conversion in ovarian slices treated with gonadotropin (34). Dempsey and Hill induced a marked increase in the urinary titer of estrogen in a man with a feminizing adrenocortical tumor by the administration of chorionic gonadotropin as well as with pregnant mare serum (49).

It is worth noting also that in chorion-epithelioma of the testis high urinary titers of gonadotropins as well as of estrogens have been reported and it has been claimed by Martin and Carden that the estrogen was produced by the interstitial cells under the influence of gonadotropin (47). Of further interest

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are the observations that the administration of clomiphene to the human subject results in both an increased urinary excretion of gonadotropins as well as of estrogen although the causal relationship of these findings is not yet established (44-46).

In congenital adrenocortical hyperplasia associated with virilization there is an increased elaboration of androgen. Part of this fraction is converted to estrogen, for the urinary titer of estrogens is increased (11), but the conversion ratio must be relatively small since the clinical manifestations reflect the overproduction of androgen. In the so-called adult or "acquired" form of the virilizing adrenogenital syndrome there is, for as yet unknown reasons, although it too may be genetic in origin, a preferential utilization of the androgen pathway in contradistinction to the aldosterone and cortisol pathways (2) and thereby a facilitation of the formation of androgen (36). The pathogenesis of the "acquired" type is presumably not related to inadequate 21-hydroxylation as is the case in the congenital form of virilization. In this latter, the deficiency of cortisol production leads to increased adenohipophyseal corticotropin secre-

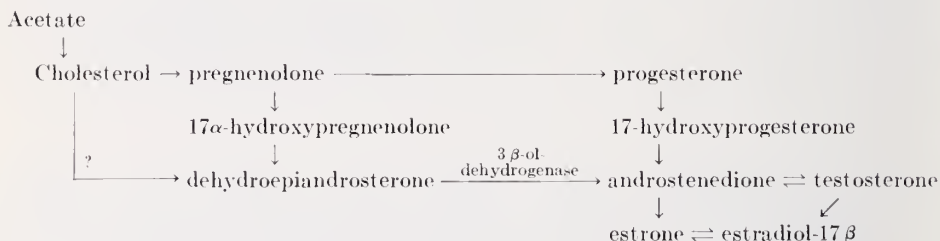


FIG. 1. Schema of androgen and estrogen biosynthesis in the adrenal cortex and gonads.

tion, increased formation of pregnenolone, progesterone and 17 α -hydroxyprogesterone and a subsequent pouring of these precursors into the androgen pathway (2). As with the congenital variety, the conversion of androgen to estrogen in the adult form of virilizing adrenogenital syndrome must be relatively small if a virilizing syndrome ensues.

On the other hand the conversion of androgen to estrogen by the adrenal cortex may be so great as to result in a feminizing adrenogenital syndrome. This may be seen in the male particularly in association with adrenocortical tumors (12) or even with non-tumorous adrenocortical hyperplasia (37). The biosynthetic pathways in the former have been delineated by us (13) in a recent study. In the female pure feminization due to tumor has been reported by Snaith in a 5½ year old child (14) and the adult feminizing adrenogenital syndrome is presently under study in our laboratory (15). The syndrome of adrenal feminization in the female due to either acquired or congenital adrenocortical hyperplasia has not been recognized but it is likely that in the adult it might easily be overlooked. In the child, it will be necessary to examine all instances of so-called constitutional sexual precocity in whom no urinary gonadotropins are found.

The possible biosynthetic defects in Klinefelter's syndrome have been dis-

cussed by us elsewhere (16). In essence it has been suggested that there is an increased conversion of androgen to estrogen in the testes possibly due to a primary rather than secondary increase in the production of gonadotropins. It is postulated that the decrease in the local concentration of androgen in the testis results in the tubular alterations observed, and the increased elaboration of estrogen produces the gynecomastia. The more striking testicular manifestations seen in the chromatin positive group may be then due to the probably greater conversion of androgen to estrogen in subjects with an XXY chromosome type as opposed to an XY karyotype.

In the syndrome of functional prepuberal castration there is a high urinary titer of gonadotropins and gynecomastia. The urinary excretion of neutral 17-ketosteroids may be normal or increased. As discussed by us elsewhere (17), the suggested pathogenesis is an absence of the testes, increased pituitary gonadotropin secretion, facilitation of the adrenal androgen pathway under the influence of luteinizing hormone with increased conversion of androgen to estrogen. The latter is the presumed cause of the gynecomastia.

It is of great interest that interstitial cell tumors of the testes, although presumably autonomous, result in virilization prepuberally whereas postpuberally a large number of such tumors result in a feminizing syndrome (18). It would thus seem wise to group or characterize functional testicular tumors and disorders biochemically as virilizing or feminizing as well as on pathologic and anatomic grounds. The difficulty with the latter mode of classification is that the normal or usual biosynthetic pathways associated with any cellular structure may be altered in disease. For example in the adult with an interstitial cell tumor, one would expect, on the basis of histology, increased androgen secretion rather than an effective predominance of estrogen elaboration resulting in feminization. It is precisely the biochemical perspective that focuses one's attention on the fact that alterations have occurred in the normal physiologic function of the cell under study.

Analogous considerations apply to ovarian disorders. Virilism is seen in association with 1) Stein-Leventhal ovary, 2) hilus cell tumor or hyperplasia and, 3) arrhenoblastoma. We have demonstrated that in the arrhenoblastoma there is an increased production of androgen, *i.e.*, androstenedione as well as testosterone (19). In these incubation studies, no estrogen was obtained with progesterone C-14 as a precursor indicating not only an increased production of androgen but a decrease in the conversion to estrogen. When androstenedione is the chief androgen produced by the arrhenoblastoma, virilization is probably associated with high urinary titers of neutral 17-ketosteroids whereas when the more potent testosterone is the main androgen elaborated, the urinary titer of neutral 17-ketosteroids is probably normal or low. Similarly production of testosterone by a virilizing ovarian lipid cell tumor has recently been demonstrated (20) as well as by a follicular ovarian cyst (40). Savard has suggested that normally the ovarian follicle is concerned with estrogen production whereas the ovarian stroma is concerned with androgen elaboration (50).

It has been demonstrated that the Stein-Leventhal syndrome is associated

with increased plasma and urinary titers of testosterone. The present evidence, obtained from incubation studies, would suggest that the defect in the Stein-Leventhal syndrome is an inability to convert androstenedione and testosterone to estrogen (21-23, 28, 32). Greenblatt and his associates (23, 24) have suggested that there may also exist a 3β -hydroxy dehydrogenase deficiency resulting in a failure of conversion of dehydroepiandrosterone into other androgens and ultimately estrogens. Although there is no evidence at present it seems

TABLE I

	Increased androgen (?conversion normal?)	Increased conversion androgen → estrogen (with or without increased androgen)	Decreased conversion androgen to estrogen
Male			
Adrenal cortex	Adrenogenital virilism <i>tumor</i> <i>hyperplasia</i> {congenital acquired	Prepuberal castration (functional) Adrenogenital feminiz- ing syndrome due to tumor or hyper- plasia	
Testis	Interstitial cell tumor (child)	Klinefelter's syndrome Interstitial cell tumor in adult (?Sertoli cell tumor)	
Etiology?		?Puberal gynecomastia	
Female			
Adrenal cortex	Adrenogenital virilism <i>tumor</i> <i>hyperplasia</i> {congenital acquired Stein-Leventhal ovary	Adrenogenital feminiz- ing syndrome tumor ?hyperplasia ?Sexual precocity	?Post menopausal hir- sutism?
Ovary	Arrhenoblastoma and vir- ilizing ovarian tumors Stein-Leventhal syndrome	Tumor granulosa cell theca cell	Stein-Leventhal syn- drome ?Arrhenoblastoma

likely that similar mechanisms are at work in the virilizing syndromes associated with either hilus cell tumor or hyperplasia.

On the other hand feminizing syndromes will be seen especially with tumors in which the cells are capable of increased conversion of androgen to estrogen (31) because of increased quantities of the facilitating enzymes. Granulosa cell tumors and particularly feminizing lutein cell tumors are thus also best regarded from the biochemical viewpoint rather than from a pathologic-anatomic perspective.

It would, therefore, seem logical to view many of the disorders of the gonads and adrenal cortex of a sexual nature as being concerned with the ratio of conversion of androgen to estrogen and the clinical manifestations as reflecting such increased or decreased conversion (Table I). The alterations in conversion

ratio, particularly by the adrenal cortex, are reflected not only in those overt syndromes already discussed but also in less obvious clinical pictures. For example overproduction of androgens or estrogens by the adrenal cortex in the male may result in alterations in the testes. The testicular picture ranges from spermatogenic maturation arrest to marked fibrosis and hyalinization of the testes with absence of the Leydig cells (12, 25, 26). It is conceivable that, since some of these changes observed in the patient with hyperplasia are reversible by cortisone, adrenocortical hyperfunction results in suppression of pituitary gonadotropin including luteinizing hormone. The beneficial effect of cortisone is to induce corticotropin suppression and thereby a decrease in adrenal production of androgen and estrogen. As a consequence, indirectly, pituitary gonadotropin secretion or release is facilitated and normal testicular function is restored.

It would follow that the analogue of this is encountered in that form of the Stein-Leventhal syndrome secondary to adrenocortical hyperfunction in which improvement occurs following the administration of cortisone or a glucocorticoid. In this light the findings of Roy *et al.* (33) are of interest. They noted that the administration of dehydroepiandrosterone or of Δ_4 -androstenedione resulted in cystic ovarian changes.

However, there is evidence that there are two types of Stein-Leventhal syndrome, a primary ovarian form as well as that secondary to the adrenogenital syndrome (39). In both, there ensue pathologic changes characterized by arrested follicle maturation and anovulation. It is thus possible that in the primary ovarian type there is an intrinsic defect in the ovary in respect to its ability to convert androgen to estrogen in contrast to the altered ovarian biosynthetic capability secondary to abnormal adrenal androgen or possibly estrogen secretion which in all likelihood is exerted via an effect on pituitary luteinizing hormone secretion. In this latter group, Kase *et al.* were unable to demonstrate an increase in ovarian androgen production but they did not attempt to study the conversion of androgen to estrogen (39).

A final word might be added about puberal gynecomastia. It is possible that this may result from the temporary overproduction of estrogen from androgen in the testes or adrenal possibly due to a temporary overproduction of luteinizing hormone. In a sense it would represent a mild reversible form of a disorder similar biochemically to that seen in either the feminizing adrenogenital or in Klinefelter's syndrome. Testicular biopsy studies might indirectly, perhaps, shed some light on the disorder.

Although there are as yet many deficiencies in the evidence to establish these formulated concepts, the hypothesis explains and helps classify many of the clinical disorders encountered and is capable of experimental verification or disproof.

SUMMARY

An hypothesis based on alteration in the androgen-estrogen conversion ratio is presented for the classification of many of the adrenocortical and gonadal clinical sexual disorders. It is suggested that a biochemical perspective

may afford a more rational understanding of these disorders than a purely pathologic-anatomic viewpoint.

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Out-Patient Care of Orthopaedically Handicapped Children

A Demonstration Project (1959-1962)*

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The purpose of this project has been to analyze the various factors involved in continuity of care of the child with orthopaedic handicaps. An attempt was made to define more clearly the scope of responsibility of the professional, paramedical and administrative staffs in a hospital out-patient service, and to develop feasible techniques of rendering comprehensive care.

The role of each participant in the clinic was studied individually and analyzed in detail. Many different techniques were tested, and where feasible, the results were subjected to statistical evaluation. Those observations that could not be analyzed statistically were evaluated as to the efficiency with which the specific needs of the children were met medically and socially. Although the orthopaedic out-patient department at The Mount Sinai Hospital functions as an integrated service, this report will describe the individual roles of each member of the clinic staff. This evaluation included consideration of maximum utilization of professional time, the co-ordination of professional and paramedical personnel, the development of an efficient "team" approach in the total care of the child and the simplification of administrative procedures.

Medical and social needs, philosophy of medical practice and administrative procedures vary greatly in different communities. It is impossible, therefore, to evolve one type of comprehensive care service that is universally applicable. By presentation of the experiences of each medical and paramedical person involved, as well as administrative data, it is hoped that individual findings might be applicable to orthopaedic and other out-patient facilities in urban or rural communities, and that the "team" approach might stimulate public health and medical personnel toward improvement and expansion of services for the handicapped child.

BACKGROUND

Preventive medicine has traditionally been directed toward the elimination of the causative factors of disease. Decreasing exposure to virulent organisms, or increasing resistance immunologically has brought tuberculosis, smallpox, diphtheria, poliomyelitis and other scourges under control. Since the etiology of many handicapping conditions in children is unknown or beyond control,

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these traditional techniques cannot be applied. For example, congenital and developmental defects, endocrine and metabolic diseases and crippling effects of trauma may be responsible for severe disability. One of the major challenges facing the orthopaedic surgeon is the development of methods to minimize the handicapping effects of musculoskeletal deformities. It is to this aspect of "preventive medicine" that this demonstration project has devoted its attention.

The effectiveness of total care for the handicapped child depends upon the degree of understanding of the problems of the child, the quality and co-ordination of medical and paramedical facilities and the continuity of care. In orthopaedic surgery, perhaps more than in most specialties, early recognition of a pathological condition affords the clinician his best opportunity to obtain maximum therapeutic results. A child born with a hip dislocation, for example, has an excellent chance of developing a normal hip if treated early, but a poor chance if diagnosis is delayed until the child begins to walk and a limp is noticed.

In New York City, the Health Department, with the assistance of outstanding professional medical and paramedical personnel in the community, and the use of advisory committees, has set standards for care of the handicapped child (1). The standards have had two main purposes: 1) establishment of minimum requirements for approval of an institution desirous of participating in the Medical Rehabilitation Program, and 2) statement of general principles outlining an "ideal" service to provide a guide toward which hospitals could strive in the improvement of existing services. As a result, many different approaches and techniques have been developed to render comprehensive programs for the handicapped child in New York City. These depend upon the community needs of different sections of the city and the wide variety of types of medical and hospital services available.

Regardless of apparent differences in programs, certain basic principles have evolved and have been accepted as being a definition of a high caliber of total care for the handicapped child. With this definition as a baseline, survey teams reviewed the hospitals participating in the Medical Rehabilitation Program (2). The findings were reported to the Advisory Committee of each specialty (orthopaedic surgery, cardiac surgery, cleft palate, pediatrics, otology, ophthalmology, etc.), composed of specialists in the particular medical field, and community leaders in all medical and paramedical areas relating to the handicapped child. The recommendations of these Advisory Committees formed the basis for approval or disapproval of the institution, as well as a guide to the institution as to weaknesses in its program. This technique has resulted in significant improvement of care for children with physical handicaps in New York City (3).

Recent medical advances, such as the use of antibiotics, vaccines, and improved public health measures, have resulted in the decline in incidence of many chronic conditions such as osteomyelitis, tuberculosis and poliomyelitis, and have controlled many complications that might have led to pro-

longed hospitalization (4). Concomitant improvement in public health nursing, special educational facilities, vocational services and welfare programs have permitted earlier discharge of patients from hospitals. As the number of children being treated in in-patient facilities declined, and those treated as out-patients increased, it became evident that improved out-patient facilities for handicapped children would be required. In 1957, the Health Department surveyed twenty orthopaedic out-patient clinics in New York City, and explored the status of out-patient services. On the basis of the published observations (5) a *Guide* (6) was developed expressing a philosophy of standards for out-patient care of the orthopaedically handicapped child. Many of the theoretical concepts expressed in that *Guide* form the basis of the present investigation which is, in part, an inquiry into the practical validity of those concepts.

METHODS

This study was conducted over a three-year period (April 1, 1959—March 30, 1962) in the Department of Orthopaedic Surgery of The Mount Sinai Hospital. This 1,200 bed voluntary hospital has a fully approved residency training program in orthopaedic surgery as well as in related medical specialties (pediatrics, obstetrics, medicine and psychiatry), and an excellent physical medicine, social service and nursing staff. Rather than attempting to develop the "ideal" type of demonstration clinic, the project was designed as an experimental investigation of individual techniques and methods employed in the out-patient department. An attempt was made to evaluate aspects of the program for total care of the handicapped child including early case finding, co-ordinated medical and paramedical services and continuity of care. Where the experimental method could be measured statistically, the study was planned for that type of evaluation. Because of the nature of some of the problems investigated, only qualitative evaluations could be made.

At The Mount Sinai Hospital two children's orthopaedic clinics are held weekly, accepting children up to the age of seventeen from all areas of the city. Fees are charged according to ability to pay, but no patient is denied admission to the clinic because of inability to pay. Visits average 4,000 per year.

ORGANIZATION

Medical Staff

A. *Orthopaedic Surgeon.* The extensive effort and time required to complete the curriculum of surgical, basic science, research, trauma and children's orthopaedic training in the hospital often delegates the care of the ambulatory and "less severely ill" patient to a position of secondary importance. Although the ambulatory patient will occupy the major portion of his time and attention in practice, and be his major source of case finding and early diagnosis, the resident is generally less interested in the clinic patient because of the "non-surgical" and "non-acute" nature of his problems. It is the responsibility of the chief and orthopaedic attending staff to view the clinic as an important

part of the service as a whole, both for resident training in ambulatory orthopaedics and continuity of care of the patient.

It is generally agreed that where active teaching is an important part of a residency program, a higher caliber of medical care results. Three basic types of teaching techniques were tested in the clinic: didactic, patient-oriented, and conferences. Although limitation of time and space in the clinic did not permit formal didactic teaching sessions there, examples of material discussed during the didactic portion of the three-year residency program were demonstrated constantly to the resident staff, utilizing out-patients who presented these conditions. Individual patient-oriented teaching was found to be most effective when conducted simultaneously with patient care. "Teaching" as it related solely to the orthopaedic condition was incomplete, and did not give the resident an understanding of the need for continuity of care. Prescribing a brace, for example, without taking into account parental acceptance and understanding, the child's habits and pediatric history, the home and school situation, etc., frequently resulted in failure of treatment because the appliance was not used.

Residents examined all new and old patients and conferred with the attending orthopaedic surgeon. According to the classical technique of "clinic coverage," the resident consults the attending only in problem cases. When this method was evaluated it was found that the resident staff was not guided in observations and diagnostic techniques and frequently "experience" consisted of repeating the same errors. The most effective patient-care teaching technique was the active participation of the attending orthopaedic surgeon during resident examinations, histories, discussions, and planning of regimens of care. In addition valuable information was gained as to the maturity of the resident and his progress in the training program by checking the parent's understanding of the nature of the child's illness, and the purposes and details of the treatment outlined. The entire resident group was called together to discuss interesting patients and points of examination. The presence of an attending orthopaedic surgeon playing an active teaching role in the clinic and working closely with the residents permitted many major decisions to be made without unnecessary in-patient admissions.

Since the clinic was generally extremely busy, convening conferences at the time that problems arose resulted in long waiting periods for the other patients. When a patient presented a complex problem he was asked to remain until the end of the clinic session. Where this was not practical, the next appointment was made toward the end of another clinic session when interested personnel (physiatrist, pediatrician, social worker, or other medical specialist) who were not present routinely, could attend. These conferences served as teaching sessions in the "team" approach, and permitted exchange of ideas in rendering co-ordinated care in complicated cases.

A well-integrated program in which residents attended both in- and out-patient department activities was found to be the most effective link in continuity of care. Close continuity was best maintained when, on discharge from the hospital, or on the first visit to the clinic, the patient was assigned to a

particular resident who spoke to the family, discussed the treatment or follow-up course, and personally examined and treated the patient in the clinic at each visit. When problems arose between appointments, it was easy for the patient to contact "his" doctor and maintain a personal relationship throughout treatment. Even at final follow-up, it was the same resident who presented the patient to the staff for evaluation.

Specialty clinics (clubfoot, scoliosis, etc.), which were staffed by attending orthopaedic surgeons with particular knowledge and interest in these conditions, permitted better continuity of care, better teaching of residents, as well as co-ordination with paramedical services.

B. *The Pediatrician*. He is the most important person in the early diagnosis of orthopaedic handicaps (7). He performs the first complete physical examination of the newborn child and follows him through infancy and childhood. It is the responsibility of the orthopaedic surgeon to train the pediatrician so that he can detect positive or suspicious signs of congenital deformity or developmental disease.

In most hospitals pediatricians obtain their orthopaedic training by observing in-patients who are receiving complicated and highly specialized orthopaedic care (surgical, casts, etc.). This is often supplemented by didactic lectures and demonstrations. The most effective pediatric training technique demonstrated in this project was the assignment of a pediatric resident to the orthopaedic clinic. The resident became part of the regular clinic and participated in examination and discussion of patients. He learned to detect early signs of orthopaedic handicaps and became familiar with diagnosis and practical management of simple ambulatory pediatric orthopaedic problems that would be seen in his office practice. Not only was there universal satisfaction with this technique of training, but referral of significant orthopaedic problems from the pediatric service increased, while referral of simple "physiologically normal" conditions decreased. An initial problem that arose was the tendency to ask the pediatrician to examine children in order to avoid visits to the pediatric clinic. This resulted in a miniature pediatric clinic and no instruction in orthopaedics. Although a technique has not yet been developed, it is probably ideal to have both pediatric and orthopaedic care rendered at the same time and place.

The pediatrician's presence was invaluable in detecting problems relating to growth and development and overt pediatric conditions that generally go unrecognized in an orthopaedic clinic. The pediatrician helped to train the orthopaedic resident while he himself learned ambulatory pediatric orthopaedics.

In addition, a "check-list" type of examination was taught to the pediatric residents by means of Kodachrome films and clinical demonstrations to emphasize the need for repeated complete orthopaedic re-examination of the infant and young child. Pediatricians were encouraged to go through this check-list on each general examination. Its importance was documented during this study by examples and statistics of certain conditions 1) not present at

birth which may develop or become obvious at a later date, and 2) the clear-cut diagnostic signs of deformity which may not be easily recognizable on examination of the very young child. It was important to emphasize that an initial examination demonstrating an apparently "normal" child too often blinds the pediatrician to the possible development or manifestation of an orthopaedic condition at a later date.

C. Consultation with Other Medical Specialists. Impersonal referral and failure of the parent to understand the purpose of a consultation often led to long delays and broken appointments. These were minimized by administrative facilitation of prompt referral, preferably to a particular doctor in the specialty clinic who had worked with the team, and careful explanation by the orthopaedist to the parent of the reasons for the consultation. On return from the consulting clinic the same orthopaedic resident resumed medical responsibility for the child. Where possible, such as instances requiring physical medicine consultation, personnel normally present in the hospital would come to the clinic to see the child, thus avoiding one or two extra visits (8).

Nursing

On both in- and out-patient services the nurse plays a significant role in carrying out medical orders and insuring the success of prescribed medical therapy (9). A large part of nursing time however is generally expended in nonprofessional administrative efforts such as answering telephones, calling patients into the examining rooms, making new appointments, obtaining charts, filling out forms (x-ray, lab test, etc.) and functioning as a traffic manager, which far outweigh her nursing duties (10). This inquiry attempted to redefine her role in the clinic and to develop techniques whereby maximum use could be made of her professional skills. This was made possible by the introduction of a new category of individual to the clinic team, an administrative assistant, in whom was vested the responsibility for all administrative duties formerly performed by the nurse as well as by other clinic personnel.

The first step was to obtain a competent and interested nurse and to train her in principles of ambulatory orthopaedics. This was accomplished by having her present during examinations of patients and discussions with parents as well as by explaining to her the significance of specific observations, purposes of treatment and outlined goals. It then became possible for her to function more effectively in her professional capacity and as an effective teacher to the student nurses. In addition to her medical responsibilities the nurse's most significant roles were: a) as parent counselor and b) as liaison with community agencies.

A. Parent Counselor. A survey of parents, at various stages in their children's treatment, indicated that few had a clear understanding of the basic nature of the medical problem, why the child was being treated, and the reasons for the prescription of a certain type of therapy. Lack of understanding as to the purposes and goals of the treatment was one of the most common causes of failure of the treatment itself (broken appointments, laxity in following orders

for manipulation, braces and exercises, etc.). The responsibility for conveying this understanding to the parent rests with the examining and treating physician. However, the parent's fear and apprehension while in the presence of the doctor, language barriers, distractions in the presence of a restless child or siblings often contributed to a breakdown in communications. Before the child left the clinic the nurse conferred with the parent as to her comprehension of what the doctor had said and checked this against the doctor's note on the chart. When a new brace was received, for example, the mother was asked to apply the brace and demonstrate its use. The nurse would then clarify any points that were not completely understood and would be certain that the mother recognized the purpose of the treatment and the need for follow-up visits. If problems arose where further clarification was required, the physician would again discuss the problem with the parent. Because parents were generally more relaxed in the presence of the nurse than the doctor, it was often possible for her to determine when public health or visiting nurse referral was necessary. If the social problem exceeded her capability, the nurse either called upon the social worker for assistance or referred the patient to the worker.

B. Liaison with Community Agencies. Close contact with community nursing and therapy services which work with, and understand the philosophy and techniques of the clinic is an essential part of the nurse's duties. This contact insured continuity and success of the prescribed treatment. Regular reports from the community agencies in writing and by telephone permitted the clinic nurse constant awareness of problems as they arose (re-bracing, casts, etc.) between clinic visits.

Recommendations by the Visiting Nurse led to improvement of methods of parent instruction and counseling, and an awareness of common obstacles in the home that might interfere with the success of certain types of treatment. The community nursing and therapy personnel were encouraged to visit the clinic as a further link in continuity of care.

Counseling of parents by the nurse in the newborn nursery appeared to improve the attendance of children referred from the nursery for orthopaedic care or observation. The need for this type of service was suggested as a result of interviews of a large number of new mothers who after being referred from the nursery, brought their infants of six to eight weeks of age to the orthopaedic clinic. Most of the parents had little or no understanding of why they had been referred. Reaction varied from the feeling that the visits were unnecessary, since there was often no visible physical defect, to extreme fear that there might be a "hidden" defect that was serious.

Social Worker

The social worker in the medical setting is an essential member of the treating team, and shares in the responsibility for the success of medical therapy (11). Rehabilitation of the child often requires not only treatment of his orthopaedic defect, but also attention to his social, educational and emotional

situation as it affects or is affected by his medical problem. Among the factors interfering with the success of medical treatment in which the medical social worker may play an important role are: the reaction of the child and his parents to the problem, existing financial difficulties, interrelationship problems which affect the medical direction, pertinent cultural patterns conflicting with medical and social planning and a lack of knowledge regarding the utilization of community resources.

This project attempted to define the most effective use of the social worker in a pediatric orthopaedic out-patient department. It was found that one social worker assigned to both the in-patient and out-patient service (rather than separate hospital and clinic social workers) made for closer continuity of care.

An attempt was made to determine whether instruction of clinic personnel in early recognition of social problems that interfere with the success of medical treatment might improve patient care. Prior to each clinic session the social worker reviewed the medical charts of new patients to determine the family make-up, ethnic background, income level, source of referral, and care that the child was receiving in the hospital or clinics. Of the 57 charts reviewed it was found that the ethnic background for this group was 54.5% Puerto Rican, 35.1% Negro, 10.4% other. This distribution of patients was typical of the current hospital population in the general pediatric clinic, thus indicating no special circumstances for the orthopaedic clinic. Seventy-five per cent of the patients came from within a forty-block radius of the hospital. Sources of referral covered a broad spectrum of agencies, the most frequent of these being the New York City Department of Health Orthopaedic Consultation Service, and Mount Sinai Emergency Service. The social worker was present at the medical interview, examination and discussion with the parents of each of these patients, as well as with some revisit patients. She utilized problem situations such as apparent parent or child anxiety reaction, lack of understanding of results of the examination, or difficulty in communication, as demonstration opportunities. She explored the problem with the patient and/or parent to determine their understanding of the situation and ability to follow through with recommendations. Each situation was discussed with the physicians and nurses and, where indicated, ongoing social service care was instituted. This technique made the physician and nurse more aware of signs of problems of the patient and his family, helped to dramatize the concept of medical team care of the orthopaedically handicapped child, and assisted in making more realistic plans for future treatment and management of the patient. Its success, which was obvious to all members of the team, was demonstrated by the relatively few situations where the Visiting Nurse reported any problems in the home which had not been anticipated in the clinic. As a result of this study the social worker was able to compile the following general outline of questions, to serve as a guide to clinic personnel, that might elicit information as to a patient's and/or family's understanding of orthopaedic conditions and their implications:

1. What do you understand about the condition?
2. What precautions, if any, need to be taken?
3. What limitations are there on daily living?
 - (a) It is important to stress normal activity.
 - (b) When the child is of school age, the kind of schooling (regular class, special class or home teaching) and possible time involved should be specified.
4. What is the expectation for cure or handicap?
5. What will treatment consist of and where will it be given?
6. If an appliance is needed, how will it affect patient and family?

The social worker, therefore, came to serve as an "instructor" to the rest of the team in case finding and management of social factors as they related to the basic medical problems. When these problems could not be managed by physician-nurse conferences, the social worker was consulted for her professional assistance. This role of the social worker must be reinitiated with each turnover of resident staff.

An important general observation is the difficulty that most patients and their families have in taking the initiative in raising questions about the medical condition, its implications, or the treatment or social planning suggested. Anticipation of these problems by an alert clinic "team" and careful explanation by the physician, nurse and social worker, must be coupled with assurance that adequate understanding has been achieved by the patient and/or family.

During this project the social worker listed community facilities and services available to children with orthopaedic handicaps that were most commonly utilized at this Hospital. This list is now available to all clinic personnel and has been helpful to attending physicians in their private practices. Although a general survey of community gaps was not attempted, some areas of need for resources were readily apparent. These include: transportation to clinic of the severely handicapped child, payment for visits and special services (casting) on an out-patient basis, group educational opportunities for the severely handicapped child to supplement home teaching, and group recreational activities for the severely handicapped child who so often becomes isolated from his peers.

The presence of a social service case aide in the clinic stimulated more efficient processing of forms and requests for shoe and brace prescriptions, camp placement, etc., and helped to curtail waiting time for patients.

Administrative Assistant

Analysis of the administrative duties performed by the nurse, social worker, and physician revealed that these nonprofessional involvements took time from professional care and were not co-ordinated.

The administrative assistant functioned as the liaison between the in- and out-patient, as well as the follow-up services, co-ordinating the many different facets of activity in the clinic itself. She relieved the nurse of her administra-

tive responsibilities and supervised the work of the clerk and volunteer. She became the "traffic manager," being sure that the proper cases were assigned to each physician and that the "clinic flow" was smooth. She made the appointments, kept cardex files which contained necessary information for follow-up of each patient, was personally responsible for follow-up, was available to parents for telephone contact, checked charts for the clinic, planned the size of the patient load for each session, co-ordinated x-ray, laboratory and consultation services, supervised the messenger and clerical services and, in general, became the administrative manager of the clinic, under the direction of the chief of the clinic. The administrative assistant served in this same capacity on the ward service, where she co-ordinated administrative services and maintained statistics and diagnostic files. She knew the patients and families, and with a resident and social worker participated in discharge plans and follow-up arrangements.

This project clearly demonstrated that when in-patient, ambulatory, and follow-up care is administrated by a single individual, a greater degree of continuity and co-ordination is possible when compared to methods where the administrative aspects of a patient's care are rendered by the efforts of a number of professional and nonprofessional individuals.

The following duties were found to be effectively carried out by, or under the direction of the administrative assistant, relieving the nurse, resident, and social worker for professional services:

1. Charts: a. Check on missing charts. b. Assign charts to doctors. c. Arrange for laboratory tests.
2. X-rays: a. Check on missing x-rays. b. Send for x-rays during clinic session. c. Arrange for x-ray file to be in clinic for each appointment. d. Arrange for the taking of x-rays.
3. Call patients into examining rooms.
4. Administratively record services rendered (*e.g.*, cast appliances).
5. Answer telephone.
6. Interview new patients for vital statistics for clinic records.
7. Have physician check charts on all children who missed appointments to determine importance of follow-up.
8. Make and change appointments.
9. Send new appointment when an appointment is missed.
10. Record follow-up data and "tag" patients sent to other clinics for consultation. (These patients often do not return to the referring clinic because of misunderstanding, poor communication, or administrative problems of a large out-patient service.)

ADMINISTRATIVE PROCEDURES

Appliances

When braces are ordered, instead of sending the patient to the bracermaker with a written prescription, it was found essential to have the braceman measure the child in the clinic (so he fully understood the doctor's orders), deliver

the braees to the clinic, and be present at "checkout." This technique permitted the braecman to obtain first-hand instructions as to alterations or special features, avoided many revisits to a braee shop, and prevented lack of understanding on the part of the parent which frequently led to failure of the child to use the appliance. The presence of the braecman served as an excellent teaching technique for the resident as well as the attending staff.

X-Rays

By careful planning and co-operation with the X-Ray Department, administrative methods were developed to facilitate roentgen examination on an emergency, interval, or "cast change" basis as well as co-ordinate availability of x-rays with patient visits.

Appointment System

Most clinics attempt to limit the daily patient load by some type of appointment system. In many out-patient departments the time assigned for registration is the same for all patients. This time is often as long as an hour or two prior to the beginning of the clinic session itself to permit obtaining charts and x-rays and to be certain that patients are there when the doctor arrives. Since patients are usually seen on a "first come, first serve" basis, many arrive even earlier.

A system where each patient was given a specific time for a clinic appointment was not found to be feasible. When patients failed to appear, doctors wasted time waiting for them. When a doctor was called away for an emergency or was delayed, his patients were not seen. Also, since varying periods of time were required for different patients and conditions, and time was often taken out for group demonstration and discussion of problem patients, a "time" schedule was relatively ineffective.

The most satisfactory technique was found to be division of the clinic into two sessions, "early" and "late." The efficiency of this method depended upon the administrative assistant who spoke to the parents and made appointments at a time that was realistic for clinic and patient. Too often appointments given arbitrarily conflict with personal commitments (*i.e.*, calling for other children at school, feeding time of other infants, etc.) and cannot be kept. Once the appointment was set, the chart and x-ray could be obtained before the clinic session so that all records were in the clinic when the patient arrived.

Children assigned to the "early" session were examined during the first hour of the clinic. Even if a patient did not appear, physician's time was not wasted since the number assigned for that period made allowances for the percentage of broken appointments generally noted in the clinic. Similarly, "late" appointments were seen during the second hour. The cast room was in operation simultaneously, and had its own "early" and "late" roster.

Follow-Up

Since it was considered that a major responsibility of the treating agency was to insure as far as possible the success of prescribed treatment, the proj-

ect included an investigation of various types of follow-up efforts that a clinic might make to aid and encourage completion of treatment.

A special follow-up card provided data to evaluate the effectiveness of different follow-up procedures. The following data was recorded: name, address, phone number, clinic chart number, business address and telephone number of father, or friend or relative of family, school, child health stations attended, referral agency, data of visit. Each new appointment was recorded and the date was circled when the appointment was not kept. A notation for each correspondence was made. The resident reviewed the charts of all patients who failed to attend to determine whether the medical condition warranted further efforts at follow-up. The degree of follow-up effort depended upon the physician's evaluation of the severity of the condition and the medical need for further care.

Follow-Up Groups. At the time of the first visit to the clinic patients were placed alternately into one of the following groups:

Group A. Maximum follow-up effort. A patient in this group would not be discharged for lack of attendance unless he had failed to respond with a visit to a postcard, a phone call when possible, and a certified letter. This cycle, or that part of it necessary to produce a visit, was repeated after each missed appointment.

Group B. No follow-up. The initiative in requesting a new appointment, after having missed a visit, was left entirely to the parents of the patient. If a new appointment was not made the patient was discharged for lack of attendance.

As the project progressed other follow-up groups were established.

Group C. Patients received a hospital-addressed stamped postcard and were instructed verbally and in writing as to use of card to obtain new appointment.

Group D. Same as C but verbal instruction was omitted.

Group F. Same as C but patient had to supply postage stamp.

Group N. Maximum follow-up effort expended. This group was composed of children referred from The Mount Sinai Hospital's newborn nursery.

Discharge Categories. When his attendance at the clinic was terminated, or when an appointment was missed, each patient was classified by the clinic physician into one of the following categories:

Category 1. Maximum benefit achieved—discharge by the clinic physician at the completion of observation or treatment program.

Category 2. Terminated clinic attendance prematurely—in this category the clinic physician felt that the condition had improved to such an extent that clinic follow-up was no longer indicated.

Category 3. No observation or treatment program necessary—the clinic physician made this determination after the first or second visit.

Category 4. Patient transferred to another agency or known to have left the city.

Category 5. Discharged for non-attendance at the clinic—this determination was made after a four-month interval since the last visit. Patients in this category were considered as requiring further care.

Category 7. Still under treatment at the end of study period, having attended the clinic for over a year with a good record of attendance and with frequent visits.

Category 9. Still under treatment at the end of the study period, having a poor attendance record or with few visits made.

Each patient was considered as either a success or a failure on his completion of his therapy program. Some patients were considered in a neutral group, *i.e.*, those for whom no further treatment was necessary (Category 2). The value of the follow-up activities was evident regardless of whether those who achieved part of the treatment goal were considered as neutral or success.

From the statistical evaluation based on these criteria it was evident that simple follow-up efforts (new appointments sent by clinic) resulted in a sig-

TABLE I

Distribution of the 1,357 Patients Registered with the Pediatric Orthopaedic Clinic May 1959 through December 1961, by Assignment of Patient to Follow-Up Group, and by Type of "Discharge" of Patient by Clinic Physician

Discharge Category	Total	Follow-Up Group					
		A	B	C	D	F	N
	1,357	302	258	111	105	46	535
1—Treatment completed	367	95	66	19	19	—	168
2—No additional follow-up indicated	147	41	30	8	4	1	63
3—No treatment necessary	177	22	15	10	15	5	110
4—Transfer to other treatment agency	70	14	6	2	3	1	44
5—Premature termination of treatment	428	73	116	56	50	19	114
7—Under care at end of project after a long period of consistent attendance	131	55	23	10	8	2	33
9—Under care only a short while at end of project	37	2	2	6	6	18	3

nificant increase (approximately 23%) in the number of those completing treatment, compared with the control group where no follow-up efforts were expended. When patients were considered a "success" (completed care) or "failure" (discharged because of failure to attend the clinic), it was demonstrated that for those receiving maximum follow-up efforts (Group A) 67% were successful while for the other follow-up groups (no follow-up) 34-43% were considered successful. It is interesting that there was no increase in the number of patients completing treatment by providing a hospital-addressed stamped postcard or giving oral and written instructions for obtaining a new appointment.

Although the follow-up efforts outlined above resulted in a significant increase in the eventual number of patients returning to the clinic, this program to increase the per cent of children completing the treatment program not only increased clerical time devoted to follow-up, but also decreased visit-broken

appointment ratio. It is significant that in the groups that completed, compared with those that failed to complete the program, there were a greater number of missed appointments in that group where follow-up efforts were expended. For example, in the follow-up, of those who completed the treatment program there were 4.4 visits per missed appointment, while in the group without follow-up there were 9.5 visits per broken appointment. There were 0.8 visits per broken appointment in the group that failed to complete the treatment program and who received follow-up, while those without clinic follow-ups had made 2.0 visits per broken appointment. These observations indicate that when patients are aware that the clinic will send a new appointment if they fail to keep one, they are more prone to break their appointments.

It was also noted that the per cent of broken appointments and follow-up observations were similar regardless of the diagnosis, and regardless of whether the condition itself represented mild, moderate, or potentially severe handicaps.

Approximately 85% of all revisits were made as scheduled or at another appointment requested by the parent. The group in the category of clinic follow-up A (maximum follow-up effort) who completed the treatment program made 90% of the clinic visits on their own initiative. These may have failed an appointment and requested a new one themselves. Another 7.5% of the visits were made after one correspondence. An additional 2% came after two or three further letters. This indicates that maximum gain results from a single follow-up effort and is a guide as to the results that can be expected by the techniques used in this study.

The quality of clinic care depends primarily upon maintaining continuity by "preventing" broken appointments rather than solely establishing an efficient method of follow-up of broken appointments. Factors which cannot be measured statistically play a major role in encouraging patients to return. Some of these are courtesy, interest, punctuality and patience on the part of the medical and paramedical staff, cleanliness and privacy, pleasant waiting areas, recreational facilities, "call-in privileges" by the patients when problems arise, consideration when appointments are made as to their convenience for the parents, etc.

ORTHOPAEDIC CONSULTATION SERVICE

The New York City Health Department Orthopaedic Consultation Service (12) has been located at Mount Sinai Hospital since 1956. This clinic which is staffed by an orthopaedic surgeon and pediatrician was established as a case-finding agency. It affords consultation to child health, school health, other medical agencies and private physicians in situations where orthopaedic abnormalities are suspected and the patient cannot afford private consultation. This service avoids the usual complex details involved in clinic referral, offers a more personal consultation, and stimulates early case-finding.

Breakdown in continuity of care of this valuable case-finding technique was explored during the course of the project. It was discovered that when an

appointment to the orthopaedic consultation service was missed, as long as six months might elapse before the referring agency recognized that the child had not been seen. If no effort was made by the parent to seek another appointment, there was no mechanism in the consultation clinic to follow-up the broken appointment. One hundred sixty children were referred for orthopaedic consultation during the first quarter of 1959. Of this number 56, or 35% failed to keep their appointment. Of 104 patients who received consultation, 59% were referred for treatment, indicating the effectiveness of the clinic as a case-finding technique. Of 49 patients who failed to keep their appointments at the orthopaedic consultation service, almost half never obtained a consultation, emphasizing the need for a follow-up system in the present orthopaedic consultation service and in future orthopaedic consultation clinics that might be developed in other boroughs.*

An effort was made to demonstrate whether close co-operation between the Orthopaedic Consultation Service and a treatment center to which the children were referred might prove effective in increasing the percentage of children who would undertake and complete the prescribed treatment program. All children referred to the Orthopaedic Consultation Service by health stations in the neighborhood of The Mount Sinai Hospital, and who were in need of therapy, were referred to The Mount Sinai Hospital Pediatric Orthopaedic Clinic and were asked to register for this clinic immediately after the orthopaedic consultation. Of the 43 children in this category seen in the Orthopaedic Consultation Service during three months of 1960, only 14 or 32% kept the original appointment. However, after follow-up activity by The Mount Sinai Hospital Orthopaedic Clinic was initiated, 88% of the patients began a treatment program. This is in contrast with the results of the survey of the 1959 orthopaedic consultation service population, where it was demonstrated that no more than 67% of the referred patients ever began a treatment program.

OTHER CONSIDERATIONS IN STUDY

(1) Evaluation of "early vs. late" referral. Records were maintained to determine which orthopaedic conditions could have been detected at an earlier date, had the examining and responsible medical agency been more alert to early signs of orthopaedic disease. Review of these records served as a guide in training pediatricians within the hospital and community.

(2) *Nursery Liaison.* Correlation of the findings noted at birth with those subsequently noted in the clinic, in patients referred from the nursery, clari-

* As a result of the findings of this project, it was suggested to the Bureau of Handicapped Children of the New York City Department of Health that a follow-up system be initiated in The Orthopaedic Consultation Clinic. Since completion of the project and during preparation of this report such a system has been begun (April 1963). When an appointment to the Consultation Clinic is missed the referral agency is notified and requested to make another appointment for the patient. Preliminary observations indicate that during the short period that this system has been in effect the percentage of patients receiving consultation has risen from 65% to almost 90% of those referred.

fied many medical concepts that served as a guide in evaluating those signs and symptoms of orthopaedic disease that are significant, those that should be continued under observation, and those findings that may be considered normal. Since it is common to observe attitudinal situations in the immediate postpartum life, as well as normal joint tightness during the first few days, these suspicious findings were noted and were observed in subsequent examinations (13).

First-hand instruction in diagnosis of orthopaedic conditions of the newborn was accomplished by assignment of an orthopaedic resident to the nursery to examine all newborn infants with each new pediatric resident. Significant statistical increase in referral of orthopaedic abnormalities to the clinic resulted.

COMMENTS

Patient-oriented teaching conducted simultaneously with patient care under the supervision of an attending orthopaedic surgeon was found to be the most effective method of instruction in clinical orthopaedics for orthopaedic and pediatric residents. This technique was an impetus for improving the attention that patients received and apparently simultaneously improved the caliber of care.

Assignment of a pediatric resident to the orthopaedic clinic permitted instruction in the types of orthopaedic problems most frequently encountered in office and hospital out-patient practice, thereby stimulating early diagnosis and offering instruction in management of simple musculoskeletal problems.

A "check-list" type of infant orthopaedic examination was devised. Since many orthopaedic conditions become manifest after early infancy, the need for re-examination of infants at 6 and 12 months of age was established. More realistic criteria than had been available previously were developed as to whether infants with apparent orthopaedic conditions required early treatment, continued observation, or no treatment.

Sub-specialty clinics were organized to permit children with certain orthopaedic disabilities such as club foot, scoliosis, or hip dysplasia to be followed by one attending orthopaedic surgeon with special interest and experience in the particular field. This technique proved very effective in patient treatment, follow-up and resident training.

Unnecessary hospital admissions were avoided by the presence of an attending orthopaedic surgeon in the clinic for discussion and major decision-making, and by more complete out-patient workup.

The same resident following both hospitalized and clinic patients permitted an effective link in continuity of care, and enabled the patient to be treated by the same doctor throughout his in-patient and out-patient hospital course. It also established personal contact between the patient and "his" doctor.

Conferences with parents as to the nature of illness, purpose of therapy and

prognosis were held by the clinic physicians and nurses. During the period that this technique was employed in the clinic, it apparently contributed significantly to the reduction of the number of broken appointments and in the increase of active parent co-operation in treatment (bracing, exercises, etc.).

When patients with complex medical, social, educational, vocational and habilitative problems were given special appointments after the clinic sessions more time was available for complete discussion of the case by the entire team.

The most important of the basic professional duties of the nurse in a pediatric orthopaedic clinic include: counseling of parents and patients, assisting physicians, checking on use and care of appliances, checking of feasibility of treatment outlined in relation to home, family and emotional factors, determining need for social service referral, teaching students, carrying out inter-agency referrals.

When the medical social worker regularly attended clinic sessions, there was a general increase in the awareness of all clinic personnel of the importance of collaborative effort in the treatment of the pediatric orthopaedic patient.

The use of the social service case aide, serving as one of the regularly assigned clinic personnel, resulted in curtailed waiting time and less traveling within the hospital for patients, more effective processing of appliance requests and fewer instances where patient did not follow through with obtaining appliances.

The social worker developed a training technique to increase the clinic personnel's alertness to signs of possible difficulty which might affect the success of medical treatment.

It was noted that it was difficult for most patients, or their families, to take the initiative in raising questions about the medical condition, its implications, the treatment itself, or social planning. A general outline indicating the areas and patterns of most initial concern to patients and/or parents was developed for the use of other team members, in their examination and treatment, so that potential problems might be anticipated and prevented.

A list of community resources most commonly used by the patients and the types of assistance these services provide was developed as a guide and was made available to clinic personnel and to attending physicians.

A study of some of the social characteristics of the patient population provided information regarding the patient group, and indicated some areas for possible further investigation.

The presence of a new category of clinic personnel, the "administrative assistant," in the clinic freed the professional staff from nonprofessional duties and allowed more time for examination, treatment and parent-counseling by the nurse and physician. The administrative assistant assumed responsibility for management of the nonprofessional aspects of the clinic, liaison with other hospital departments and arrangement of an appointment system.

The attendance of the braceeman at the clinic sessions facilitated ordering, measuring and adjustment of appliances and avoided unnecessary extra clinic visits and misunderstandings that prevented proper use of appliance.

An "early" and "late" appointment system proved to be the most feasible technique in cutting down patient's waiting time and in keeping the clinic running at capacity without overloading.

The largest gain in sending for patients to return for further treatment came with only one correspondence. However, when the physician felt that the child's condition was of sufficient importance to require further treatment, it was found that a number of patients who did not respond to a single correspondence could be brought back after a certified letter was sent to the home, or Public Health or Visiting Nurse referral was made.

In the group of patients for which special follow-up procedures were established, 67% completed treatment to the satisfaction of the doctor whereas in the other groups only 34-43% of patients fell into this category.

It was apparent that prevention of broken appointments could be increased by courtesy, interest and patience, cleanliness and privacy, recreational facilities in pleasant waiting rooms, telephone call-in privileges when problems arose and consideration of parents' convenience when appointments were made.

Special follow-up efforts, which resulted in increase of number of patients returning to clinic and completing treatment, required extra clerical time and increased the "broken-appointment" to "kept-appointment" ratio.

The concept of continuity of care was employed where consultation with other specialties was required. After the consultation the administrative assistant made certain that the referring orthopaedic surgeon again saw the patient and discussed the consultation findings with the parent.

Although the specific medical problems of the patient were the primary concern of the orthopaedic and the entire clinic staff, it was demonstrated that only by a "team" approach could co-ordination of medical, paramedical, administrative and community services, and continuity of care be accomplished.

SUMMARY

This report outlines the results of an investigation of techniques for improving out-patient care in the children's orthopaedic clinic of a large urban voluntary hospital. An attempt was made to design a program for total care of the handicapped child, including co-ordinated medical, paramedical and community services, early case-finding and continuity of care. Each facet of clinic and personnel operation was analyzed to define and clarify the roles of the professional and ancillary staffs.

The material is presented briefly in this report in a manner so that it might be used: 1) as a guide to planning or improving co-ordinated pediatric orthopaedic out-patient services in an urban community or, 2) separate findings,

when applicable, might be abstracted and utilized in individual out-patient programs.

A new category of clinic personnel, the administrative assistant, was established and her role in the management of the clinic, and the assumption of responsibility for nonprofessional duties, formerly performed by the professional staff, is reviewed.

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Co-existent Pheochromocytoma and Thyroid Carcinoma (Sipple's Syndrome)

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The concurrence of pheochromocytoma and thyroid cancer has been established recently as a significant phenomenon (1). It is the purpose of this report to record two new cases, to add a follow-up note on a third one, and to review the literature.

Case 1. L.Q., a 65 year old Chinese cleaning-man, was admitted to the Neurological Service (192404) with a history of dizziness, blurred vision and ptosis beginning eight days before and soon followed by rapidly progressive weakness of the upper and lower extremities. On neurological examination, he showed complete loss of ocular movements with fixation of pupils to light and accommodation. Caloric stimulation of the labyrinth showed no response. The gag reflex was diminished and dysarthria was pronounced. Muscle fasciculations were noted on chest and thighs. Power was markedly diminished in all extremities, more so in the proximal musculature. Deep tendon reflexes were abolished. Testing of vibration and position senses revealed faulty perception below the level of the clavicles. Electromyograms disclosed lower motor neuron involvement.

Other findings of note were inability to expectorate bronchial secretions and a blood pressure of 150/60 mm Hg. Significant laboratory findings were a white cell count ranging to 19,000 with 89% neutrophils, an erythrocyte sedimentation rate (Westergren) of 80 mm per hour and a spinal fluid protein which rose from 33 to 139 mg per 100 ml. No porphobilinogen was found in the urine.

The patient was treated with tracheostomy and broad spectrum antibiotics for his chronic pulmonary disease. While the neurological disorder improved somewhat, the pneumonia did not respond adequately and he succumbed after one month. The final clinical diagnosis was diffuse myeloradiculopathy and brain stem encephalopathy, presumably infectious (30).

Autopsy (19908) disclosed advanced bronchiectases, moderate cor pulmonale and atrophy of the liver. Numerous sections from the central and peripheral nervous system failed to show findings of significance, a not uncommon occurrence in such disorders. Two incidental observations, however, were made at autopsy. A firm, ovoid, pale-tan nodule, 2 cm in greatest dimension, in the left lobe of the thyroid, proved to be a follicular carcinoma arising within a benign colloid adenoma (Fig. 1). The right adrenal contained a soft, spheri-

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cal, gray tumor, 0.7 cm in diameter, exhibiting minute hemorrhages. Microscopically this was a typical pheochromocytoma which was surrounded by focally thinned cortex. (Figs. 2, 3). Step sections prepared from the pituitary failed to reveal an adenoma.

The following two cases were found in the files of the Johns Hopkins Hospital, Baltimore:

Case 2. S.B., a 60 year old Polish born man, was brought to the emergency room of the Johns Hopkins Hospital in 1939 in a comatose condition after he fell and struck his head. A subdural hematoma was evacuated but he died

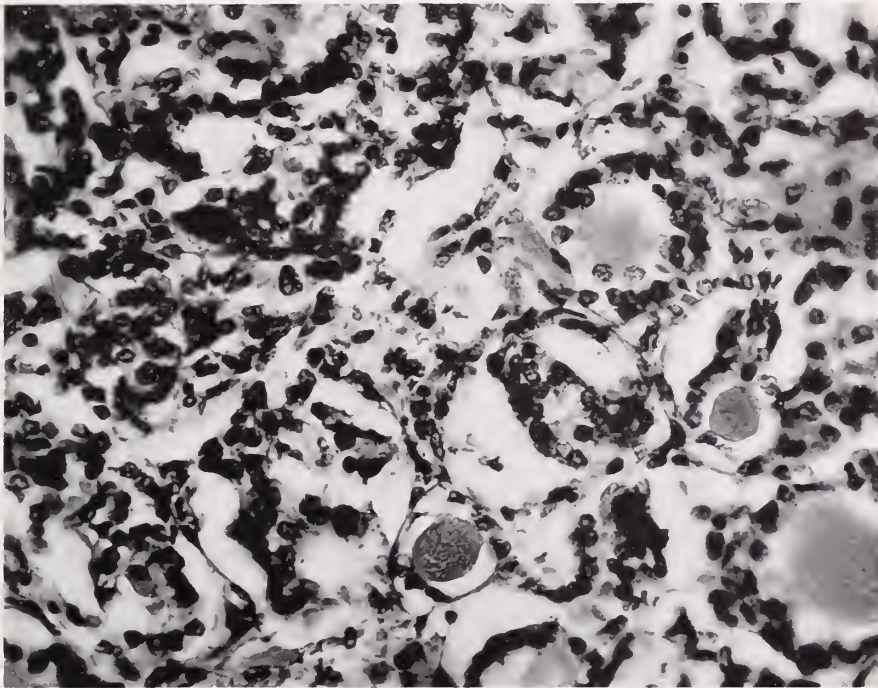


FIG. 1. Thyroid gland showing follicular carcinoma. Hematoxylin and eosin $\times 300$.

three days later of bilateral pneumonia. At autopsy (16429), both adrenals were replaced by sizable pheochromocytomas (Lt 75 g. Rt 60 g). Cortical adenomas were also present. The heart was considerably enlarged reflecting hypertensive heart disease. The right lobe of the thyroid was enlarged by firm whitish nodular tissue which was also found in the left lobe. Wet tissue was still available and new sections were prepared which showed the thyroid tumor to be carcinoma with amyloid stroma (Fig. 4). Because of the long storage in formalin none of the special stains for amyloid (Congo Red, Methyl Violet, Thioflavin T) are positive. In order to obtain additional information, the patient's widow was contacted who stated that the father of the deceased had died in middle age of a thyroid cancer.

Case 3. Actually not a new case but the same patient who was reported by Beer *et al.* (3) and later by Hyman and Mencher (4). This woman, who had a previous pheochromocytoma removed from the left adrenal, had recurrence of her symptoms for which she was admitted to Johns Hopkins Hospital in 1946. A grapefruit-sized pheochromocytoma of the right adrenal was successfully removed. The patient was lost to follow-up studies.

The distribution of pheochromocytoma in the tabled cases is of interest. While bilateral adrenal pheochromocytoma occurs in 7 to 10 per cent of adult cases, it was found in 12 out of 16 cases when thyroid carcinoma co-existed. Of note is concurrent adenomatous involvement in four instances of one or

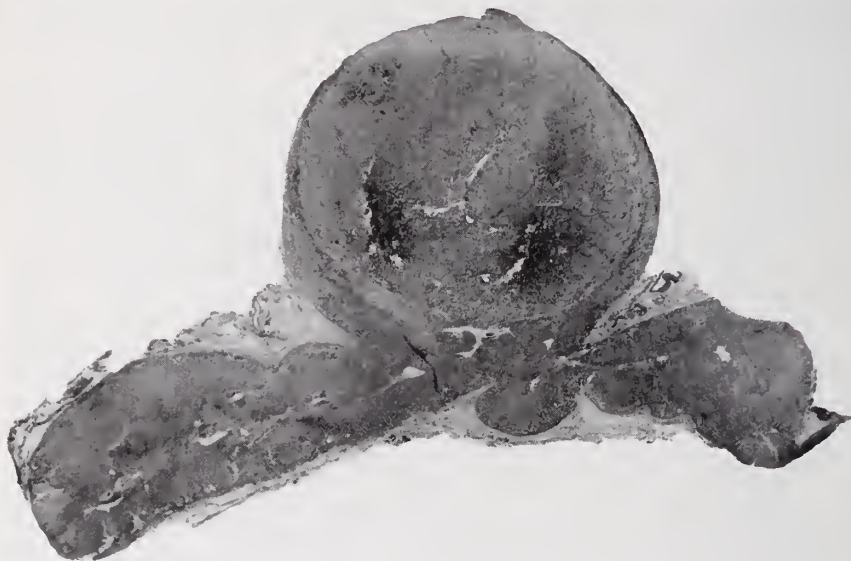


FIG. 2. Right adrenal gland with spherical pheochromocytoma. Hematoxylin and eosin $\times 4.5$.

more parathyroid glands, usually silent clinically. Although the histological type of thyroid cancer was variable, it is worthy of mention that the rare medullary carcinoma with amyloid stroma occurred five times and showed familial involvement. The rarity of co-existent pheochromocytoma and thyroid carcinoma is attested by the fact that in 20,000 consecutive autopsies at the Johns Hopkins Hospital, 33 thyroid carcinomas and 16 pheochromocytomas were found, only once (Case 2) in the same patient.

DISCUSSION

It is only recently that the co-existence of pheochromocytoma and thyroid carcinoma has been recognized not to be fortuitous. Although De Courey and De Courey (15) observed a considerable, possibly significant, number of pa-

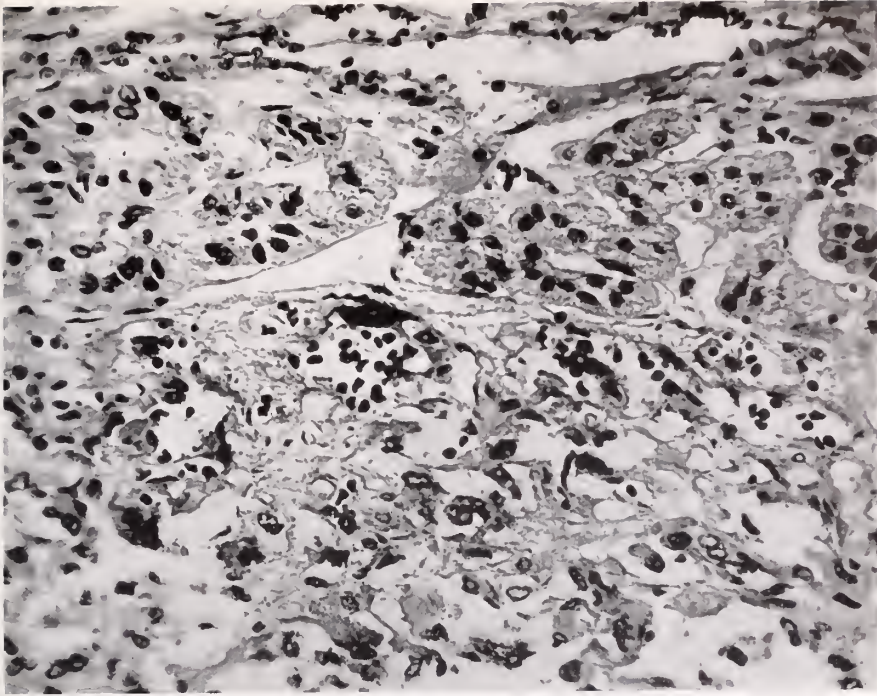


FIG. 3. The lower half of the field is occupied by the pheochromocytoma, the upper part by thinned-out cortex and fibrous capsule. Hematoxylin and eosin $\times 300$.

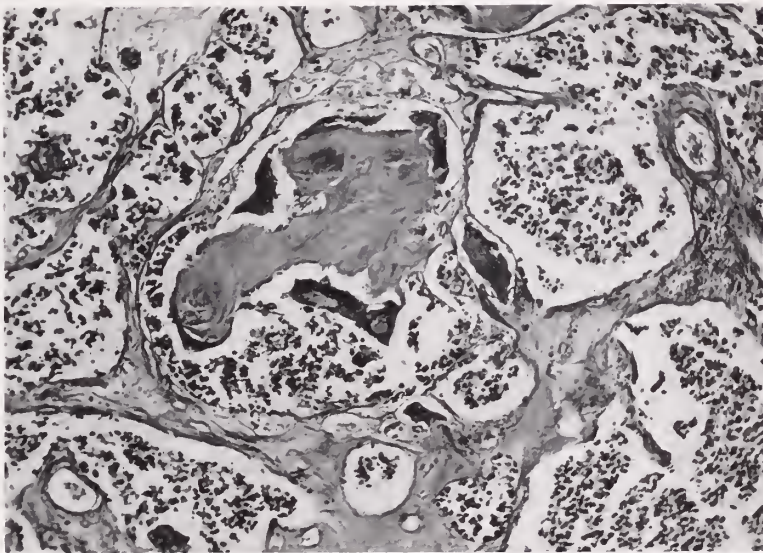


FIG. 4. Bands and masses of amyloid traverse the thyroid carcinoma. Four giant cells of the foreign body-type surround the amyloid deposit in the center of the picture. Hematoxylin and eosin $\times 100$.

TABLE I
Cases of Thyroid Carcinoma with Concurrent Pheochromocytoma

Author Year	Age Sex	Clinical Features	Adrenal Lesion	Thyroid Lesion	Comment
Eisenberg 1932	63f	Thyroid enlarged for 10 years with pain recently. Marked weight loss in 3 weeks before admission. Normal blood pressure.	Bilateral malignant. Widespread metastases.	Papillary carcinoma. No metastases.	Autopsy: death due to spread of malignant pheochromocytoma.
Beer <i>et al.</i> 1937 Hyman and Mencler 1943	26f	Throbbing headaches, nausea, sweating, fatigue, peripheral vasoconstriction led to thyroidectomy 9 years before. Symptoms persisted after removal of adrenal tumor, blood pressure dropped from 280/200 to 110/70 mm Hg. Patient cured.	Left side. Right side (1946). See Case 3 of text.	Papillary carcinoma.	Mother and sister had thyroidectomies. Another sister with a similar clinical picture died after thyroid surgery. A niece had a pheochromocytoma removed.
Muntz <i>et al.</i> 1947	39f	Six years before right hemithyroidectomy for palpitations, tachycardia and weakness. Some 2 years later episodes of increasing sweating, tachycardia, tingling of scalp, vomiting. Blood pressure fluctuating to 320/190 mm Hg.	Bilateral containing 2.3 g epinephrine	Bilateral adenocarcinoma with metastases to cervical and mediastinal nodes.	Autopsy.
Rothermich 1952	25f	Nodular goiter resected 5 years before. (Adenocarcinoma with regional lymph node metastases.) Treated with radiotherapy. Typical adrenergic attacks for 5 or 6 years. Admitted in moribund condition with ventricular tachycardia.	Bilateral.	Adenocarcinoma surgically resected. No recurrence.	Autopsy: death due to isolated myocarditis with heart failure.

Dick <i>et al.</i> 1955	44m	Episodic shivering, diarrhea and vomiting. Palpable tumor above left kidney. Symptoms abated after resection of adrenal tumor. Left cervical mass appeared 18 months later.	Left side.	Carcinoma developing in adenoma.	Patient alive.
Freedman <i>et al.</i> 1958	34f	Recurrent attacks of headaches, palpitation and weakness for 12 years. Diffuse goiter; thyroidectomy 10 years before admission. Blood pressure ranged up to 240/220 mm Hg. Pheochromocytoma resected. Death 4 years later.	Left side.	Bilateral anaplastic carcinoma with metastases to cervical nodes and both adrenals.	Autopsy.
De Graeff <i>et al.</i> 1959	37f	Frequent episodes of headache, palpitations, sweating, and dizziness with fluctuating hypertension (220/140 mm Hg.) for 5 years. Right adrenal tumor resected. Patient remained hypertensive and died the next day.	Bilateral. Also multiple small retroperitoneal pheochromocytomas.	Anaplastic carcinoma with pulmonary metastases.	Autopsy.
Shipple 1961	33m	Admitted for intracranial hemorrhage. Long history of occasional severe headaches. Death following craniotomy.	Bilateral.	Bilateral follicular carcinoma.	Autopsy: (?) adenoma of parathyroid.
Cushman 1962	55m	Cervical lymph node 24 years before (carcinoma). Subtotal thyroidectomy 8 years later (? carcinoma). Long history of "migraine headaches" with pallor, weakness and diabetes. Patient died of cerebral hemorrhage following carotid sinus denervation.	Right side.	Medullary carcinoma with local amyloid. Metastases to neck, lung, liver, spleen.	Autopsy: adenoma of parathyroid. Family history (see next case).

TABLE 1—Continued

Author Year	Age Sex	Clinical Features	Adrenal Lesion	Thyroid Lesion	Comment
Sabay 1962	37m	Long history of infrequent "migraine headaches" with nausea, pallor and sweating. Thyroid nodule removed 18 years before (medullary carcinoma). Ten years later removal of pheochromocytoma which manifested itself by paroxysmal hypertension, positive phentolamine test. Present admission for recurrent thyroid carcinoma.	Left side.	Medullary carcinoma with local amyloid.	Son of previous patient. This patient's daughter (age 12) has also, medullary carcinoma of thyroid. Her urine catecholamines are not elevated.
	29f	History of several months of severe frontal headaches accompanied by dilated pupils and cold extremities. Blood pressure ranged up to 210/160 mm Hg. Enlarged nodular thyroid. Death after laparotomy.	Bilateral.	Moderately differentiated thyroid carcinoma with widespread metastases.	Autopsy.
Manning <i>et al.</i> 1963	28f	At age 18 bilateral pheochromocytomas removed because of episodic hypertension (248/180 mm Hg.) with concomitant palpitation, tachycardia and blurred vision. Present admission for vertiginous attacks and blood pressure of 160/120 mm Hg. Positive histamine and phentolamine tests. Reoperation showed recurrence of tumor on right side with many satellite nodules. Enlargement of right lobe of thyroid.	Bilateral.	Bilateral medullary carcinoma with amyloid stroma.	Functioning multiple chief cell adenomas of 4 parathyroid glands. There are 2 siblings who had bilateral pheochromocytomas removed.

O'Brien (*) 1963	21f	Total thyroidectomy 7 years before death.	Bilateral.	Medullary carcinoma with amyloid stroma. Metastatic to hilar nodes, lung and liver.	Autopsy. Death following cesarean section for placenta praevia.
	28m	Sudden increase of right-sided neck swelling present for the past 5 years. Biopsy showed adenocarcinoma which was treated with radioactive iodine. Some 5 years later, readmission for spells of pounding headaches with palpitation, sweating and hyperventilation and hypertension with increased urinary catecholamine excretion. Laparotomy for removal of adrenal tumor; incidental liver biopsy.	Right side.	Metastatic adenocarcinoma in liver (biopsy).	Patient alive.
Finogold and Haddad 1963	27m	Cachexia, thyroid enlargement. Multiple lytic bone lesions. B.P., 127/70 mm Hg. Thyroidectomy. Death one week later.	Bilateral (?) Small.	Anaplastic carcinoma with lymph node and bone metastases.	Autopsy: two parathyroid adenomas (nephrocalcinosis). Father of patient had bilateral pheochromocytomas resected.
Present Case 1	65m	Admitted for unrelated neurological disorder. Asymptomatic thyroid and adrenal tumors.	Right side.	Follicular carcinoma arising in adenoma.	Both tumors represent incidental autopsy findings.
Present Case 2	60m	Admitted with craniocerebral trauma. Died of pneumonia.	Bilateral.	Bilateral medullary carcinoma with amyloid stroma.	Both tumors represent incidental autopsy findings. Father died of thyroid cancer.

* This author mentions a case of functioning parathyroid adenoma in the presence of a pheochromocytoma.

A case of a 54 year old woman with bilateral pheochromocytoma and a thyroid "adenoma" was presented at a Clinico-Pathologic Conference (case 28-1963) New England J. Med., 268: 894, 1963. The original sections of the thyroid gland cannot be located (28). For this reason, we have omitted this case.

tients with pheochromocytoma who had diffuse or nodular goiter or thyroid carcinoma, it remained for Sipple (1) to prove statistically the validity of this statement. This author noted that 27 instances out of 537 cases of pheochromocytoma had a co-existent primary malignant tumor in another organ. Six of these, or 22 per cent were thyroid carcinoma, a tumor which otherwise comprises only 0.5 per cent of all malignancies. The incidence of thyroid carcinoma is fourteen times higher in the presence of pheochromocytoma.

It is intriguing to speculate on the interrelationship of tumors of the adrenal medulla and the thyroid by assuming that fluctuating catecholamine levels would lead to fluctuation in TSH secretion which may be responsible for hyperplastic and neoplastic change in the thyroid (1). Against this interpretation, however, is the long interval between the appearance of the thyroid neoplasm and the onset of characteristic symptoms of the pheochromocytoma in several instances. If increased catecholamines would cause the thyroid tumor, far more thyroid carcinomas concurrent with pheochromocytomas could be expected. Another argument against hormonal interrelationship is furnished by our first case in which the adrenal neoplasm, presumably because of its minute size, remained asymptomatic. It is more likely that genetic factors account for the co-existence. Fourteen families with pheochromocytoma are recorded (12, 14, 16, 17)*, one of which has multiple thyroid carcinomas (10). Concurrent pheochromocytoma with neurofibromatosis, a classical heredofamilial disorder, has been known for many years (18). More recently (19, 20), its co-existence with the von Hippel-Lindau syndrome has been emphasized, a malady which we have considered to be akin to tumors of the carotid body and other glomera well known for their heredofamilial proclivity (21).

The several parathyroid adenomas in the tabled series point to a relationship with the familial syndrome of multiple endocrine tumors, (Wermer's Syndrome) (22, 29), which in turn, overlaps with the Zollinger-Ellison syndrome (23, 24, 33).† Thyroid carcinomas have been reported in cases of parathyroid adenoma (24, 25, 32) and hyperparathyroidism in a patient with pheochromocytoma (13). The co-existence of pheochromocytoma and adrenal cortical hyperplasia or adenoma, however, is considered fortuitous (24, 27). Our first patient's son, age 44, and his three granddaughters, age 11, 10 and 6, are perfectly well. The patient's daughter and her eight children reside in China so that no information concerning them is available. As previously stated, the father of our second patient died of thyroid carcinoma.

If one follows Wermer's (29) postulates, familial endocrine adenomas are multicentric rather than solitary and would therefore appear in both partners of paired organs. The high incidence of bilateral adrenal medullary tumors in Sipple's syndrome is a strong case in point. Instances of unilateral adrenal involvement either develop the second pheochromocytoma later (Case 3) or

* We know of another as yet unpublished family observed at Bellevue Hospital, New York, N. Y.

† Wermer (31) feels that these two syndromes are not interrelated.

die of intercurrent disease (Case 1). It is more difficult to fit a malignant neoplasm such as a thyroid carcinoma into the frame of the concept of "adenomatosis" without resorting to speculation. While it would be convenient to assume malignant change in a pre-existing thyroid adenoma such as in our first case, a glance at the table will show that only once (7) a statement to this effect is made. It has to be conceded, however, that a thyroid carcinoma arising from an adenoma will soon obliterate its point of origin so that even step or serial sections through the entire growth will become unrevealing. More disturbing is the absence of other thyroid adenomas in our first case which means that the postulate of multicentricity cannot be met, an impression which is strengthened by the tabulated findings. The bilaterality of thyroid cancers frequently mentioned in the table and also found in Case 2 does not necessarily mean origin from two separate tumors. Advanced thyroid cancers commonly show this feature. Thus while Wermer's concept is a valuable one, we feel that some of his postulates are too stringent.

SUMMARY

The co-existence of pheochromocytoma and thyroid carcinoma (Sipple's syndrome) has recently been recognized as meaningful. This phenomenon, while occurring in isolated instances, appears to follow an heredofamilial pattern and to be related to other familial, multiple, endocrine adenomas (syndromes of Wermer and Zollinger-Ellison). Two cases are recorded wherein both lesions were clinically silent. A follow-up on a previously published case is given and the pertinent literature reviewed.

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The Management of Spontaneous Intracranial Hemorrhage in Non-Eclamptic Pregnancy

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The question of management of intracranial hemorrhage of pregnant patients was stimulated by the recent admission to this hospital of an eighteen year old patient who suffered a subarachnoid hemorrhage due to a vascular anomaly in the eighth month of pregnancy. Among the pertinent questions asked at that time were: 1) What should be the neurological management in terms of diagnostic procedures in the parturient patient? 2) What is the preferable mode of delivery of the baby, cesarean section or vaginal delivery? 3) And the future? Should she be allowed to become pregnant again?

Definite answers to these questions were not easily obtainable, because this problem is a relatively rare one and the experience of clinicians is consequently limited. Study of clinical material concerning nineteen patients, from the experience of neurologists and obstetricians at this institution, was found to be pertinent to this problem. An additional search of the literature revealed important data in another 149 patients.

Table I lists the patients with respect to etiology—aneurysm, arteriovenous anomaly, sinus thrombosis, and hemorrhage of undetermined origin—and with respect to the time of bleeding—prior to pregnancy, during pregnancy, during labor, and in the puerperium. For inclusion in this series, there had to be documentation of subarachnoid hemorrhage. This is so for all cases except patient #3.

Parenthetically, this report does not deal with patients who have proven aneurysms or arteriovenous anomalies which did not cause subarachnoid hemorrhage. There is abundant evidence in the literature that patients with such demonstrable congenital lesions have gone through pregnancies without any neurological complications such as subarachnoid hemorrhage.

Moreover, eclamptic patients were not studied. The differential diagnosis between this toxic-metabolic disorder and subarachnoid hemorrhage due to congenital malformations may at times be quite difficult. One of our own cases (#10), without prior knowledge of having an intracranial aneurysm, could easily have been misdiagnosed as only suffering from pre-eclampsia. Inasmuch as an aneurysm may be more prone to rupture in the presence of hypertension (1), a patient with pre-eclampsia and subarachnoid hemorrhage should be investigated for the possible presence of a vascular malformation.

SPONTANEOUS SUBARACHNOID HEMORRHAGE PRIOR TO PREGNANCY

Among the Mount Sinai Hospital cases, nine patients had spontaneous subarachnoid hemorrhage and then went on to become pregnant. Two patients

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had aneurysms, three had arteriovenous malformations, and four had spontaneous subarachnoid hemorrhage of unknown cause. The following protocols describe their clinical course:

1. C.C., age 27, para 1. At age 26, three months before admission, she was hospitalized elsewhere because of severe head pain and a stiff neck. A spinal tap then revealed bloody fluid. Bilateral carotid angiography revealed an aneurysm of the right supraclinoid portion of the internal carotid artery. The right common carotid artery was ligated. Nine days thereafter, a craniotomy was performed and a clip was placed on the aneurysm at its origin. On admission to this institution, she had a mild organic mental syndrome and a left hemimotor-sensory syndrome. Spinal fluid was clear; the protein was 40 mg%. Repeat carotid angiography revealed the hypaque passing through the clip, visualizing the aneurysm.

TABLE I
Subarachnoid Hemorrhage and Pregnancy—168 Cases
Time of Hemorrhage

Etiology	II. Before Pregnancy (Total—30 Cases)	III. During Pregnancy (Total—86 Cases)	IV. During Labor (Total—27 Cases)	V. During Puerperium (Total—25 Cases)
A. Aneurysm (Total—49)	2 (7)	2 (35)	0 (0)	0 (3)
B. Arteriovenous Anomaly (Total—19)	3 (3)	2 (10)	0 (1)	0 (0)
C. Unknown Cause (Total—96)	4 (11)	2 (35)	0 (26)	4 (14)
D. Venous Thrombosis (Total—4)	0 (0)	0 (0)	0 (0)	0 (4)

The numbers in parentheses refer to cases reported in the literature.

Six months later, she was re-admitted for a therapeutic abortion. The indication for this procedure was "an aneurysm of the Circle of Willis."

2. B.S., age 29, para 0. At age 22, she suddenly developed severe head pain, stiff neck, and vomiting. Neurological examination was normal, except for weakness of the right lower extremity. Right carotid angiogram demonstrated an aneurysm at the base of the anterior cerebral artery. A left carotid angiogram was normal.

Seven years later, she became pregnant. Her prenatal course was uneventful except for transient episodes of hypertension, the highest being 194/94. She delivered a normal baby via low forceps extraction, midline episiotomy, under cyclopropane anesthesia. The puerperium was normal.

3. C.F., age 66, para 2. At age 14, she suddenly became ill, went into a "coma," and subsequently was unable to read, write or understand what was said to her. She improved in a month's time, but her handwriting was never the same again. At age 66, she was admitted to this hospital because of poor

vision, which occurred suddenly five months previously. At that time, vision was "misty" and she could not read or write. Two months thereafter, a "confusional" episode occurred, in which she found she had sewn a sleeve to the neck opening of a garment. There was also some concurrent difficulty in memory. The neurological examination revealed a mild organic mental syndrome, a right homonymous field defect, and weakness at the right hip. The reflexes and sensory examination were normal. Carotid angiography demonstrated an arteriovenous malformation in the left parieto-occipital region. She was treated with anticonvulsants.

She had married and had two children at age 26 and age 28. Both were delivered vaginally without difficulty. In the ninth month of her second pregnancy, she had a grand mal seizure.

4. J.M., age 27, para 0. At 17 years of age, she developed a sudden onset of pin and needle sensations in the right hand and arm, then the leg and the face. Within fifteen minutes, the right leg became weak, she could not speak, and lethargy ensued. Upon admission, she was in a deep stupor; there was a right hemiplegia. Left carotid angiography revealed an arteriovenous anomaly in the region of the anterior choroidal artery and an intracerebral mass. A craniotomy was performed and an intracerebral hematoma was evacuated. A "series of clips was placed across the vessels from which this lesion was made up, and finally active bleeding stopped." "The region of the lesion was covered with muscle and on top of that gel foam."

At age 26, the question of pregnancy was raised. A neurosurgical opinion was that pregnancy was permissible, but delivery should be by cesarean section. The obstetrician decided to "play it by ear." After four hours of labor, she delivered spontaneously from below with low forceps, under pentothal anesthesia.

5. S.D., age 51, para 3. At age 25, had sudden headache and was unconscious "for several days." For three weeks thereafter, she could not speak, write, or read well. Two years later, she developed spells in which she would visualize the people she worked with and saw her surroundings as if she were in a dream. During severe attacks, she could not see "half vision"—or the right half of her body. At times, the right extremities would "jerk." Attacks would last a few seconds to a few minutes and occur sporadically once or twice in two weeks, or once in two years. Following the spell, she could have a headache and a need to sleep. The neurological examination was normal at age 47. Angiography performed at this time (recommended prior to electric shock therapy for a severe agitated depression) demonstrated an arteriovenous malformation in the distribution of the left middle cerebral artery. There has been no recurrence of hemorrhage as of age 51.

At ages 29, 30 and 32, she went through three pregnancies. The prenatal courses were normal. She delivered spontaneously with low forceps without difficulty or sequelae. After her last pregnancy, she had a tubal ligation. She became pregnant the next year and had a therapeutic abortion. At this time, a hysterectomy was performed.

6. N.S., age 26, para 2. Five years previously she had a sudden head pain associated with a stiff neck and vomiting. There were no neurological findings. No angiography was performed. She was treated supportively. There was a questionable recurrence five months after the first episode of subarachnoid hemorrhage.

She was advised that she could have children normally. The first baby was delivered two years ago, spontaneously, with low forceps. The second baby was born two months ago in the same manner.

7. M.Z., age 34, para 0. Seven years previously, she had sudden head pain, vomiting, stiff neck, and weakness of the right side of the body. No arteriography was performed. She was treated supportively and did well.

Although cautioned against pregnancy, she did conceive. It was decided to deliver her by cesarean section. Following this, out of fear of a recurrent cerebral hemorrhage, she has not allowed herself to become pregnant again.

8. D.A., age 39, para 3. At age 28, she had a sudden onset of severe head pain associated with inability to see objects in the left side of her visual field. Several hours later, she became nauseous and developed transient numbness of the left side of the tongue and left arm. The neurological examination was normal, except for lethargy, a left homonymous field defect, bilateral eyeball tenderness, and a stiff neck. A right carotid angiogram was normal. The following year, she was re-admitted because of a sudden onset of "shimmering" sensations in the right eye, dull pain behind the right eye, and a pain in the left side of the head. She then had two transient episodes of numbness, once of the left hand, then of the left side of the body. The neurological examination at this time revealed a left homonymous field defect, bilateral eyeball tenderness and photophobia, and a left Babinski sign. A pneumoencephalogram was normal.

At age 30, 32 and 35, she was pregnant. The prenatal periods were normal. She delivered normally, each time with forceps. There were no sequelae.

9. M.C., age 32, para 0. Four years previously, she had sudden head pain and blurred vision. She was unconscious for "a brief time," and was amnesic for twelve hours after the unconsciousness. She also complained of a stiff neck. The neurological examination was normal, except for "flattening" of the right face. Bilateral carotid angiography was normal, except that there was a "small linear area of contrast substance extending backward from the left carotid artery in the vicinity of the posterior communicating artery." She was treated supportively and there were no sequelae.

At age 30, she became pregnant, had an uneventful prenatal course, and delivered normally.

Combining this material with that of the literature (Table II), it may be noted that there were sixteen patients who went through uneventful pregnancies and delivered vaginally.

i. Four patients (§2, §20, §21, §22) with known histories of ruptured intracranial aneurysms delivered normally. The time interval between the intracranial hemorrhage and delivery was, respectively, seven, four and a half,

two, and two years. None of these patients had a recurrent hemorrhage. It is noteworthy that Case #20 suffered from multiple aneurysms.

ii. Two patients (#3, #5) with histories of bleeding from vascular anomalies delivered normally. Patient #3 apparently bled at age fourteen (it was stated that she was in coma but a lumbar puncture was not performed), delivered without any untoward effects at age twenty-six and, again, at age twenty-eight. The intracranial condition was diagnosed by angiography at age sixty-six, when she was investigated because of a recent history of progressive neurological symptomatology. Patient #5 suffered a subarachnoid hemorrhage at age twenty-five. She delivered normally at ages twenty-nine, thirty and thirty-two. She became pregnant again at age thirty-four and this time a therapeutic abortion was performed, but the reasons for this are unclear. She never suffered a recurrent hemorrhage, but was diagnosed by angiography when it was thought advisable to clarify the intracranial condition prior to the administration of electric shock therapy (she was in an extremely severe depression). Neither patient had a recurrence of bleeding.

iii. Nine patients (#6, #8, #9, #23, #24, #25, #26, #27, #28) with subarachnoid hemorrhage of unknown cause also delivered normally. The time interval between the intracranial hemorrhage and delivery was, respectively, three, two, two, two, two, one, unknown, unknown, two to four years. An additional patient (#29) had a cesarean section one year after a subarachnoid hemorrhage. However, a year and a half later, she delivered a second child vaginally with low forceps and a pudendal block. None of these patients had a recurrent hemorrhage. Four patients (#8, #9, #25, #27) had normal angiography. Three patients (#6, #27, #28) went through two pregnancies uneventfully. Patient #8 has had three normal pregnancies and deliveries.

iv. Six patients (#7, #29, #30, #31, #32, #33) had cesarean sections. They bled, respectively, at seven, one, four, one, five, six years prior to pregnancy. Patient #30 had an aneurysm of the left anterior cerebral artery. Patients #31 and #32 had vascular anomalies. Patients #7, #29, and #33 had subarachnoid hemorrhages of unknown cause but none of the three had angiography. Patient #30 had neurological signs and symptoms (hemorrhage?) at age six and again at age ten. Patient #29 was mentioned in an above paragraph as having had a second child by the vaginal route. Patient #32 also had a tubal ligation. Clinically, there was no apparent difference between these six patients who had cesarean sections and the sixteen patients who were allowed to deliver from below.

v. Seven patients had had neurosurgical procedures following subarachnoid hemorrhage and subsequently became pregnant. Three patients (#4, #34, #36) were allowed to deliver vaginally. The time interval between the intracranial hemorrhage and delivery was, respectively, nine, one and a half, and unknown. Patient #4 had a vascular anomaly whose feeding vessels were clipped. The neurosurgeon advised cesarean section, but the obstetrician decided to "play it by ear." She was able to deliver vaginally. Case #34 had had two previous subarachnoid hemorrhages. Craniotomy after the third hemor-

TABLE II
Spontaneous Subarachnoid Hemorrhage Prior to Pregnancy

Author	Case No.	Age Parity	Time between Hemorrhage and Pregnancy	Neurological Data	Method of Treatment	Mode of Delivery	Puerperium
Cannell and Botterell (2)	20	28 2	4½ years	Multiple aneurysms of left internal carotid artery—by angiography.	Supportive.	Low-mid-forceps under pudendal block—normal baby.	Normal.
Strohschein and Suzuki (3)	21	34 2	3 years	Sudden headache, vomiting. Right hemiparesis. Bilateral Babinski signs. Stiff neck. Angiogram—aneurysm of left middle cerebral artery.	Supportive—only had headaches during pregnancy.	Spontaneous with low forceps—normal baby.	Normal.
Heiskanen and Nikki (4)	22	48 10	2 years	Aneurysm of left middle cerebral artery—by angiography.	Supportive.	Spontaneous delivery.	Normal. Well 4 years later.
Conley and Rand (5)	23	23 multi-para	2 years	No neurologic data.	Supportive.	Spontaneous delivery.	Normal.
Cannell and Botterell (2) Laubstein, Kotz, and Hehre (6)	24	23 3	2 years	In coma with hemorrhage. Recovered.	Supportive.	Spontaneous delivery—live baby.	Normal—6 years later.
	25	24 2	13 months	Normal angiography.	Supportive.	Normal delivery.	Normal.
	26	? ?	?	Subarachnoid hemorrhage at age 19. Cause unknown. Two subsequent pregnancies.	Supportive.	1. Vaginal delivery with caudal anesthesia. 2. Spontaneous precipitated delivery at home.	Not stated.
	27	?	?	Subarachnoid hemorrhage at age 25. Normal arteriography.	Supportive.	1. Vaginal delivery with peridural anesthesia. 2. Vaginal delivery with cyclopropane.	Not stated.

sen, and Huber (7)		0	approx.	rage at age 19, had a stiff neck, and left pupil was dilated.		2. Vaginal delivery.	Normal.
Boshes and McBeath (8)	29	20	1 year?	Headache, stiff neck, bilateral Babinski signs.	Supportive.	1. Cesarean section.	Normal.
			2½ years	No angiography.	Supportive.	2. Baby delivered vaginally by low forceps and pudendal block.	Normal.
Cannell and Botterell (2)	30	29 0	4 years	Aneurysm of left anterior cerebral artery just beyond bifurcation of internal carotid artery—by angiography.	Supportive.	Cesarean section—normal baby.	Normal.
Daane and Tandy (9)	31	?	15 months	Not stated. Anomaly apparently diagnosed by angiography.	Supportive.	Elective low cesarean section under local anesthesia with penitohal.	Normal.
De Carle (10)	32	26 0	5 years	At age 10, speech difficulty and drowsiness associated with right hemiparesis and impaired swallowing. Age 6, similar but milder illness. Age 21, again right hemiparesis with hyperreflexia on right.	Supportive.	Cesarean section and tubal ligation.	Normal—follow-up report: diagnosis of aneurysm of meninges established (by angiography?).
Conley and Rand (5)	33	32 multi-para	6 years	No neurologic data.	Supportive.	Cesarean section.	Normal.
Cannell and Botterell (2)	34	24 0	20 months	Left middle cerebral arteriovenous aneurysm diagnosed by angiography.	Three hemorrhages 1950, 1952, 1954. Craniotomy—evacuation of intracerebral clot and excision of aneurysm after third episode, because of increasing papilledema and dysphasia.	Spontaneous delivery.	Not stated.

TABLE II—Continued

Author	Case No.	Age Parity	Time between Hemorrhage and Pregnancy	Neurological Data	Method of Treatment	Mode of Delivery	Puerperium
Laubstein, Kotz, and Hehre (6)	35	? 1	?	Subarachnoid hemorrhage at age 28. Laceration of internal carotid artery (by angiography?).	Carotid ligation.	Cesarean section with pentothal anesthesia.	Not stated.
		? 3	?	Subarachnoid hemorrhage at age 21. Laceration of internal carotid artery (by angiography?).	Carotid ligation.	1. Vaginal delivery. 2. Vaginal delivery.	Not stated.
Cannell and Botterell (2)	37	36 2	4 months	Aneurysm left internal carotid artery—by angiography.	Craniotomy—clipping of aneurysm.	Pregnancy terminated at 4 months on psychiatric basis.	Not stated.
		28 2	5 years	Aneurysm of left middle cerebral artery—by angiography. Two episodes of hemorrhage 8 and 3 weeks prior to admission with prolonged loss of consciousness.	1. Ligation of common carotid artery. 2. Intracranial clipping of carotid artery proximal to its bifurcation.	Therapeutic abortion and sterilization—basis "unclear."	Not stated.
Strohschein and Suzuki (3)	39	36 3	1 year	Sudden headache, stiff neck, vomiting. Diagnosis of aneurysm "substantiated" by Dr. E. Gurdjian. Shortly after missing her period, began to vomit. Then developed severe headache, vertigo, and weakness.	Supportive.	Therapeutic abortion and sterilization.	Not stated.
		25 2	1 year	Neurologic status not reported. No angiography.	Supportive.	One year later, 2 month pregnancy interrupted because of	—
Gomberg (11)	40	25 2	1 year	Neurologic status not reported. No angiography.	Supportive.	One year later, 2 month pregnancy interrupted because of	—

rhage resulted in removal of an intracerebral clot and excision of the anomaly. Normal delivery was then recommended and she did well. Patient #36 had an internal carotid artery "lesion" and a carotid ligation. She was permitted to deliver twice by the vaginal route. Patient #35 had a subarachnoid hemorrhage due to an internal carotid artery "lesion" and a carotid ligation. Her pregnancy ended in a cesarean section.

Patient #1 had an unsuccessful attempt at clipping of supraclinoid internal carotid artery aneurysm. This unfortunate result was revealed by postoperative angiography, a procedure which is now being done almost routinely by most neurosurgeons. When she became pregnant, a therapeutic abortion was recommended. It is not clear as to whether this was based on the unsuccessful surgery or the neurological condition (she had evidence of an organic mental syndrome and a left hemimotor-sensory syndrome). There were three additional patients with histories of ruptured aneurysms reported in the literature who had therapeutic abortions (patients #37, #38, #39). Patient #37 had an internal carotid artery aneurysm clipped intracranially and then a therapeutic abortion, but for "psychiatric reasons." Patient #38 had had two previous intracranial hemorrhages and a carotid artery ligation followed by intracranial clipping of an aneurysm of the left middle cerebral artery. The basis for her abortion was unclear. Patient #39 had an aneurysm but did not have intracranial surgery. She was aborted and sterilized. Patient #40 had had subarachnoid hemorrhage, the etiology of which was not delineated. One year later, when she became pregnant, she was aborted.

The above material indicates that a history of subarachnoid hemorrhage (due to aneurysm, arteriovenous malformation, or unknown cause) does not carry any extra burden with respect to pregnancy. Sixteen of thirty cases delivered normally. They neither bled in the prenatal period, during labor or the puerperium. This data must be considered in any recommendation of therapeutic abortions or sterilization for a woman who has had a subarachnoid hemorrhage—and in counseling against childbirth because of a history of intracranial hemorrhage. There are a host of factors relative to child bearing when a patient has had an intracranial hemorrhage. Case #1 had an organic mental syndrome and needed help in caring for her child born prior to her neurological illness. At any rate, a history of subarachnoid hemorrhage does not seem to contraindicate future pregnancies.

SPONTANEOUS SUBARACHNOID HEMORRHAGE DURING PREGNANCY

There were six patients seen by neurologists at this institution, who bled while in the pregnant state. Two (#10, #11) had aneurysms. Two (#12, #13) had anomalies. Two were undiagnosed—#14 because permission was not granted, #15 for unknown reasons. Their protocols are detailed below:

10. D.P., age 27, para 6. This patient was six months pregnant when, on January 24th, she suddenly developed severe headache and "epistaxis." The past history was significant in that four years ago, a diagnosis was made of a supraclinoid right carotid artery aneurysm, presumably by angiography. Blood

pressure was then 190/100. During April, before this admission, she had an appendectomy under spinal anesthesia and blood pressures were recorded as 230/162, 210/100 and 200/103. In November, when four months pregnant, she was hospitalized three weeks for hypertension, edema, and albuminuria. During December and January, she was seen five times and was always normotensive. On admission, she was semi-stuporous. There was no focal neurological findings. Blood pressure was 190/130. She developed uterine contractions and delivered a stillborn. Thirty minutes later, she was noted to have a stiff neck. Blood pressure was 160/130. Lumbar puncture—grossly bloody, pressure 330. She did well for one day in that she became alert, asked for medication, and responded to questions. It was thought she was pre-eclamptic and had perhaps also ruptured the aneurysm. In spite of routine therapy for pre-eclampsia (barbiturates, diuretics, magnesium sulfate, and Dilantin), there was no lowering of blood pressure. Because of the fear that the elevated blood pressure would result in continued intracranial bleeding, hypotensive therapy was instituted. In a matter of hours, the blood pressure dropped to normal and then to hypotensive levels (80/40). This could not be reversed by vasopressor agents. Within fifteen to twenty minutes, she went into coma and died. Post mortem was done and revealed not only visceral pre-eclamptic pathology, but also a ruptured aneurysm of the internal carotid artery.

11. L.P., age 36, para 1.* At age 28, she was in the eighth month of pregnancy, when she developed severe head pain. Two weeks later, there was a recurrence of head pain, as well as confusion and a stiff neck. Neurological examination revealed early papilledema, a right facial weakness, and a right Babinski sign. On releasing the right common carotid artery after a period of digital compression, the patient complained of a pounding pain in the head. Such pain did not occur after compression of the left common carotid artery. Right carotid arteriography revealed an aneurysm at the junction of the internal carotid and posterior communicating arteries. The right common carotid artery was doubly ligated. Ten days after ligation (and twelve to thirteen days after the intracranial hemorrhage), the membranes ruptured. Delivery was by cesarean section. She has been advised against having any further pregnancies. There has been no recurrence of subarachnoid hemorrhage.

12. L.K., age 51, para 1.† Since age 16, this patient had approximately 35 episodes of subarachnoid hemorrhage. At age 28, in the ninth month of her first pregnancy, she suddenly developed severe head pain, vomiting, and a stiff neck. Pain progressed down the spine into the legs and feet. It was a tearing, sticking type of pain. She was admitted three weeks later and spontaneously delivered a normal baby. The above-mentioned pains were said to have diminished in intensity after childbirth. One week postpartum, she again was admitted because of sudden head pain, stiff neck, and lethargy. Neurological examination revealed blurred optic discs, left facial paresis, absent right knee reflexes, bilateral Kernig sign. She did well on supportive care. However,

* This patient has been reported by Feldman, Gross, and Wimpfheimer (12).

† This patient was reported by Strauss and Tarachow (13).

relatively frequent episodes of intracranial bleeding occurred. At age 42, carotid angiography demonstrated a "cavernous angioma" in the right parietal area, which filled from the anterior and middle cerebral arteries bilaterally. At age 44, a right carotid artery ligation was done. Five years later, another intracranial hemorrhage occurred. At this time, she was left with relatively marked neurological deficit. At age 51, the last recorded episode of intracranial bleeding occurred. The sequelae to this attack were a marked organic mental syndrome, as well as a left hemimotor-sensory syndrome.

13. S.B., age 18, para 0. She was eight months pregnant when she suddenly developed severe headache, vomiting, and numbness of the right upper extremity. Three days later, double vision ensued. The images were side by side and diplopia occurred in lateral gaze. The past history may have been significant in that two months previously, she had had a spontaneous attack of low back pain, which radiated down the posterior aspect of the right leg. The neurological examination revealed a lethargic, slightly confused girl. There was a left homonymous field defect and a left Babinski sign. The neck was stiff; the Kernig test was positive. Right brachial arteriography with contralateral compression of the right carotid on one injection demonstrated the vascular supply of both carotid arteries and the right vertebral artery. There was a large arteriovenous anomaly deep and close to the midline involving the parietal and occipital areas. She did well on supportive care. One month later, she delivered vaginally with low forceps. There were no complications. Labor was about ten hours.

14. M.R., age 27, para 0. Patient was 3½ months pregnant when she suddenly developed a severe head pain and vomited. She became lethargic and her neck was stiff. The neurological examination was normal, except for the presence of moderate somnolence and a stiff neck. Arteriography was recommended, but permission for the procedure was not given. Patient did well on supportive care. However, two months later, she had a "late" miscarriage and delivered a stillborn child vaginally. Approximately one year ago, she became pregnant again, but aborted in the first trimester.

15. E.G., age 39, para 1. At age 25, during the ninth month of pregnancy, she suddenly developed severe head pain and vomiting. There was no stiff neck. In three days, the pain had almost completely disappeared, having responded well to analgesias. On the fourth day after the severe head pain, she went into labor and delivered a normal child spontaneously. Headaches returned two days after delivery. On the fourth postpartum day, a lumbar puncture revealed xanthochromic spinal fluid. It was also noted that the left pupil was dilated and a left Babinski sign was at times present. Angiography was not done. Fourteen years later, she is well. There has been no recurrence of intracranial bleeding. She was very unhappy about not having been able to have more children. Her obstetrician and neurologist had advised against this.

An analysis of the six patients detailed above and the eighty patients (Table III) in the literature revealed much valuable clinical information.

TABLE III.A
Spontaneous Subarachnoid Hemorrhage During Pregnancy (Bleeding due to Aneurysm)

Author	Case No.	Age-Parity	Duration of Pregnancy at Time of Hemorrhage	Neurological Data	Management	Mode of Delivery	Puerperium
Bleakney (14)	41	32-6	7½ months	Ten days prior to admission "queer" behavior. One week later, sudden severe headache, vomited. Admitted in coma—right hemiparesis. Left carotid angiogram revealed an aneurysm at bifurcation of internal carotid artery.	Supportive.	Low forceps, uneventful delivery under caudal anesthesia.	Normal. However, residual brain damage.
	42	46-9	10 months	Not stated.	Supportive.	Normal delivery.	Normal. Six weeks later, angiogram—aneurysm of left middle cerebral artery.
	43	32-7	9 months	Not stated.	Supportive.	Normal delivery.	Normal. Four weeks later, angiogram—right middle cerebral aneurysm. Craniotomy—aneurysm wrapped in oxyeel.
Heiskanen and Nikki (4)	44	40-2	2 months	Two months later, angiogram revealed left middle cerebral artery aneurysm.	Supportive.	Not stated.	—

							mal baby.	later, angiogram—aneurysm supraclinoid part of right internal carotid artery. Craniotomy—aneurysm ligated. Postoperative angiogram—normal.
Gomberg (11)	46	20 0	5½ months	Aneurysm at bifurcation of left internal carotid artery.	Supportive.		Cesarean section.	Normal.
Smolik, Nash, and Clawson (15)	47	25 4	9 months	Headache, convulsion.	Supportive.		Cesarean section—normal baby.	Normal. Angiography—left posterior communicating artery aneurysm. Ligation of left common carotid artery.
Strohschein and Suzuki (3)	48	35 1	9 months	Severe headache, stiff neck.	Supportive.		Cesarean section.	Well until fourth day, sudden coma and death. Post mortem—ruptured aneurysm of posterior communicating artery.
Heiskanen and Nikki (4)	49	21 1	10 months	Sudden headache. Left hemiparesis. Status epilepticus.	Supportive.		Cesarean section—normal baby.	Six hours later, respiratory arrest. Angiogram—occlusion of right internal carotid artery. Post mortem—ruptured aneurysm of right middle cerebral artery.
De Carle (10)	50	29 1	9 months	Sudden headache, convulsions, coma.	Supportive.		Cesarean section under spinal anesthesia. Normal baby.	Marked improvement in 24 hours. Well in 48 hours. Sudden recurrent hemorrhage and death. Post mortem—ruptured left communicating artery aneurysm.

TABLE III.A—Continued

Author	Case No.	Age Parity	Duration of Pregnancy at Time of Hemorrhage	Neurological Data	Management	Mode of Delivery	Puerperium
Daane and Tandy (9)	51	25 1	9½ months	Sudden headache, stiff neck, difficulty in speaking, vomiting. Did well for 5 days, then another hemorrhage with head pain. Apparent third hemorrhage during section. Died 11 hours later. Post mortem—ruptured aneurysm of left anterior cerebral artery. Intact aneurysm of left anterior communicating artery.	Supportive.	Cesarean section under local anesthesia and sodium pentothal. Live baby. Pomeroy sterilization. No oxytocics.	
Smolik, Nash, and Clawson (15)	52	25 ?	4 months	Sudden headache, stiff neck, semi-stupor. Right internal carotid artery aneurysm—by angiography.	Ligation of right common carotid artery.	Spontaneous delivery—live baby.	Normal.
	53	34	4 months	Hemiparesis, aphasia, aneurysm of anterior cerebral artery—by angiography.	Carotid artery ligation.	Not stated.	—

Decker and Rowe (16)	54	21 0	6 months	"Dizzy," sudden occi- pital pain, uncon- sciousness—recov- ered. Two weeks later, double vision on left lateral gaze. Ptosis of left lid— then dilated, poorly reactive pupil. Hos- pitalized and dis- charged. Five weeks thereafter, convul- sions, coma. Angiog- raphy revealed aneurysm of internal carotid artery at junction of left pos- terior communicat- ing artery.	Left common carotid artery ligation. Cra- niotomy—neck of aneurysm clipped.	Low forceps delivery.	Normal.
Cannell and Botterell (2)	55	35 3	5 months	Aneurysm right in- ternal carotid artery at origin of posterior communicating ar- tery—by angiog- raphy.	Ligation of common ca- rotid artery.	Low forceps delivery with pudendal block. Normal baby.	Normal. Pomeroy ster- ilization.
	56	29 3	6 months	Aneurysm at bifurca- tion of left internal carotid artery—by angiography.	Ligation of common carotid artery.	Normal delivery.	Normal.
	57	40 3	9 months	Aneurysm at bifurca- tion of left internal carotid artery—by angiography.	Silverstone clamp on left common carotid artery 4 days after hemorrhage.	Twenty-two days after clamping, low for- ceps with pudendal block—normal baby.	—
	58	33 1	8 months	Aneurysm of left mid- dle cerebral artery— by angiography.	Craniotomy—aneurysm clipped 17 days after hemorrhage.	Seventeen days after craniotomy, low for- ceps with pudendal block—normal baby.	—

TABLE IIIA—Continued

Author	Case No.	Age Parity	Duration of Preg- nancy at Time of Hemorrhage	Neurological Data	Management	Mode of Delivery	Puerperium
Brehm (17)	59	33 0	5½ months	Sudden severe head pain, stiff neck. Two weeks later, sudden unconsciousness, left hemiparesis. Right carotid angiogram—aneurysm of posterior communicating artery.	Carotid ligation.	Cesarean section—because of pelvic deformity.	Normal.
Heiskanen and Nikkí (4)	60	40 4	4 months	Second episode of bleeding, first one month previously. Angiogram—anterior communicating artery aneurysm.	Craniotomy—ligation of aneurysm.	Cesarean section.	Normal. Repeat angiogram normal.
Conley and Rand (5)	61	26 ?	6 months	Found unconscious. Developed right-sided convulsive movements. Bilateral Babinski. Right pupil dilated, unresponsive to light. Loss of vision in right eye except in upper nasal quadrant. Right anterior cerebral artery aneurysm by carotid angiography.	Craniotomy—evacuation of intracerebral clot—frontal lobe. Branch of anterior cerebral artery clipped.	Cesarean section at term.	Normal.

Cannell and Botterell (2)	63	31 0	1½ months	Aneurysm right internal carotid artery at origin of posterior communicating artery—by angiography.	Supportive.	Spontaneous abortion.	Recurrent subarachnoid hemorrhage and death, ? time after miscarriage.
	64	25 2	5 months	Aneurysm of right internal carotid at origin of posterior communicating artery—by angiography.	Supportive. Patient died of recurrent hemorrhage 17 days after initial hemorrhage.	—	—
Heiskanen and Nikki (4)	65	28 2	7 months	Angiogram—anterior communicating artery aneurysm. Recurrent hemorrhage 7 weeks later, death. Post mortem—rupture of anterior communicating artery.	Supportive pending cesarean section.	—	—
	66	23 0	8 months	Sudden headache, vomiting, urinary incontinence.	Supportive. Discharged well after 22 days.	—	—
De Carle (10)	66	23 0	8 months	Recurrent hemorrhage and comā day after discharge.	Supportive.	Cesarean section. Normal (premature) baby.	Died the following day. Post mortem—ruptured aneurysm of anterior communicating artery.

TABLE III.A—Continued

Author	Case No.	Age Parity	Duration of Pregnancy at Time of Hemorrhage	Neurological Data	Management	Mode of Delivery	Puerperium
Copelan and Mabon (18)	67	19 0	7 months	Sudden headache, vomiting, convulsions. Admitted in "decerebrate" state.	Supportive.	Vaginal delivery, with intravenous pitocin. 2½ lb. baby viable, but died in 15 mins.	Patient died 36 hours after delivery. Post mortem—ruptured aneurysm of left lentulostriate artery.
Schwartz (19)	68	23 ?	8 months	Stiff neck. Unable to answer questions. Died within 5 hours of admission. Post mortem—"aneurysm of posterior branch of a cerebral artery."	Supportive.	Post mortem cesarean section. Baby died.	—
Rhoads (20)	69	?	5 months	Comatose, papilledema. Died on 4th day of hemorrhage (this was 4th sub-arachnoid hemorrhage in 13 years). Post mortem—aneurysm at Circle of Willis.	Supportive.	—	—
Walton (21)	70	40 2	6½ months	Sudden confusion, convulsion, stiff neck. Admitted in coma, died in 6 hours. Post mortem—ruptured aneurysm at junction of left anterior cerebral and anterior communicating arteries.	Supportive.	—	—

Herzig (23)

72

34
1

7½ months

aches during pregnancy. Finally became comatose and died. Post mortem—aneurysm in right parietal region.

Supportive.

—

Richardson and Hyland (24)

73

38
5

4 months

Pre-ecclaptic, severe headache, unconsciousness, stiff neck. Two weeks later, recurrent hemorrhage with left hemiparesis and right third nerve lesion. Four weeks thereafter, third and fatal hemorrhage. Post mortem—aneurysm at junction of right internal carotid and posterior communicating arteries.

Supportive.

—

Christensen and Larsen (25)

74

32
?

7 months

Sudden unconsciousness, coma. Died in 26 hours. Post mortem—ruptured aneurysm at division of right anterior cerebral artery.

Supportive.

—

Gomberg (11)

75

26
0

5 months

Headache, stiff neck. Died within 9 hours after rapid deterioration. Post mortem—ruptured basilar artery aneurysm.

Supportive.

—

A. There were thirty-six patients who had proven intracranial aneurysms.

i. Four patients (§10, §41, §42, §43) whose aneurysms were diagnosed by angiography prior to delivery delivered vaginally. Patient §10 had both pre-eclampsia and a ruptured aneurysm. She was a difficult case to manage. She delivered a stillborn child and died in spite of treatment for pre-eclampsia and then hypotensive therapy. Patient §41 had an intracranial hemorrhage when seven and a half months pregnant. She recovered and delivered with caudal anesthesia and low forceps. Patients §42 and §43 hemorrhaged, respectively, at ten and nine months of pregnancy. After normal deliveries, angiography revealed the cause of bleeding. Patient §43 subsequently had intracranial surgery. Patient §44 had an intracranial hemorrhage due to a middle cerebral artery aneurysm in the second month of pregnancy. Her mode of delivery was not stated.

ii. Seven patients underwent cesarean section because of intracranial hemorrhage due to aneurysm. These patients did not have neurosurgical procedures. Patients §45, §46 and §47 suffered intracranial bleeding at ten, five and a half, and nine months of pregnancy, respectively. Only case §46 had angiography during pregnancy. The other two had diagnostic procedures in the puerperium and their cesarean sections may have been because the intracranial hemorrhages occurred close to the estimated time of delivery. Patients §48, §49, §50 and §51, respectively, had intracranial hemorrhages at nine, ten, nine, nine and a half months of pregnancy. Patient §48 apparently suffered no sequelae from the cesarean section and was well until the fourth day, when she suddenly went into coma and died. Post mortem revealed a ruptured aneurysm of the posterior communicating artery. Patient §49 developed respiratory arrest six hours after cesarean section and then died. Patient §50 did well for one day and then suffered a recurrent intracranial hemorrhage and died. Patient §51 had had two episodes of intracranial bleeding. It was thought that a cesarean section would be less strain on the patient, but she had a third intracranial hemorrhage during the operation. Apparently cesarean section does not necessarily protect a patient from recurrent intracranial hemorrhage.

iii. Twelve patients had neurosurgical procedures prior to delivery. Six patients delivered vaginally (patients §52, §54, §55, §56, §57, §58) after they suffered intracranial hemorrhage in the fourth, sixth, fifth, sixth, ninth, eighth months of pregnancy. Apparently the obstetricians felt that the surgical procedures protected these patients.

It is noteworthy that Case §55 also was sterilized in spite of the fact that she had a ligation of the common carotid artery. Five patients had carotid artery ligations, two had craniotomies with clipping of the aneurysms.

Patient §59 bled at five and a half months, had a carotid ligation, but then had a cesarean section (however, for obstetrical reasons).

The mode of delivery in patient §53 was not stated. The remaining four patients (§11, §60, §61, §62) bled, respectively, at eight, four, six, unknown months of pregnancy. Patient §11 had a carotid ligation followed three weeks

later by a cesarean section. Patient #60 had also bled a month previously. She had a craniotomy with ligation of the aneurysm followed by a cesarean section. Repeat angiography in the puerperium was normal. Patient #61 similarly had a craniotomy, a clipped aneurysm, and did well following cesarean section. Patient #62, however, (the fifth in this group to undergo craniotomy) had an angiogram after the second intracranial hemorrhage. The craniotomy with an attempt to clip an aneurysm was not withstood well and the patient died twenty hours postoperatively.

iv. The thirteen remaining cases died of intracranial hemorrhage. Patients #63, #64, #65 and #66 hemorrhaged, respectively, at one and a half, five, seven, and eight months of pregnancy. These four patients died of recurrent hemorrhage, which occurred at unknown, two and a half, seven, and three weeks after the initial hemorrhage. Only two of these patients were diagnosed by angiography prior to death; the remaining two were diagnosed at autopsy. The last nine patients (case #67, #68, #69, #70, #71, #72, #73, #74, #75) were admitted in almost terminal condition. They bled, respectively, at seven, eight, five, six and a half, nine, seven and a half, four, seven, and five months of pregnancy.

One post mortem cesarean section was successful, *i.e.*, Case #71. Patient #73 had had two previous hemorrhages. She was also a pre-eclamptic. Patient #69 had three previous intracranial hemorrhages over a thirteen-year period.

There is no attempt made in this paper to discuss the conservative versus the neurosurgical approach to intracranial aneurysms. The surgeons would tend to point out patients #63, #64, #65 and #66 as those who might be alive if they had had the benefit of neurosurgery. More conservative neurologists might underscore the surgical mortality of one in five patients with craniotomies as being far too high. Moreover, the recent technique of treating subarachnoid hemorrhage by careful hypotensive methods seems to be promising (43). At the present time there is a national survey in process with respect to subarachnoid hemorrhages due to aneurysm and arteriovenous anomaly. Perhaps this will provide an answer as to management in the near future. Intracranial hemorrhage due to aneurysm carries a high mortality in the series, but the 13 of 37 cases is similar to the mortality rate in the nonpregnant population. The time of hemorrhage ranged from one and a half months to nine months of pregnancy. The clinical data of spontaneous subarachnoid hemorrhage due to aneurysm in pregnancy does not seem to be any different than one would expect in the nonpregnant population. This complication seems fortuitous, coincidental and, most significantly, apparently the mode of delivery can be vaginally. Cesarean section did not lessen the chances of recurrent hemorrhage among the cases reported.

B. The above-described Cases #12 and #13, and ten patients in the literature (Table III.B), had proven vascular anomalies which bled during pregnancy.

i. Four patients (#12, #13, #76, #77) who suffered intracranial hemor-

TABLE III. B
Spontaneous Subarachnoid Hemorrhage During Pregnancy (Bleeding due to Arteriovenous Malformations)

Author	Case No.	Age Parity	Duration of Pregnancy at Hemorrhage	Neurological Data	Management	Mode of Delivery	Puerperium
Paterson and McKissock (26)	76	33 ?	8 months	Sudden coma. Partial recovery with aphasia and right hemiplegia.	Supportive.	Spontaneous delivery.	Another episode occurred two weeks after delivery. Angiography—left anterior parietal angiomatous intracerebral clot. Craniotomy—with removal of clot and anomaly. Totally aphasic and hemiplegic—unchanged two months post-surgery.
Cannell and Botterell (2)	77	28 1	5 months	Left anterior cerebral arteriovenous anomaly at upper end of central sulcus—by angiography. Right anterior cerebral artery arteriovenous anomaly, posterior portion—by angiography. Two episodes of intracranial hemorrhage in two pregnancies; in one episode, she was in coma.	Supportive.	Normal delivery.	—
	78	23 3	* 1—5 mos. * 2—4 mos.		Supportive.	Following episodes of hemorrhage, delivered at term by cesarean section.	Normal.

Pevelhouse and Boldrey (27)	79	36 2	4½ months	Left posterior cerebral and middle cerebral arteriovenous anomaly—by angiography.	Nine months after hemorrhage, excision of anomaly and clipping of right anterior cerebral artery. Two further operations and death.	Developed mild pre-eclampsia. Labor induced at 9½ months, low forceps delivery with pudendal block.	Normal. Pomeroy sterilization.
	80	17 0	4 months	Sudden headache, unconsciousness. Left hemiplegia. Bilateral carotid angiography—arteriovenous malformation 2 cm in diameter in right Sylvian fissure about 6 cm distal to the bifurcation of the right internal carotid artery.	Craniotomy—intracerebral clot removed and anomaly excised 14 days after hemorrhage.	Spontaneous vaginal delivery.	Normal.
Olivecrona and Riives (28)	81	29 ?	7 months	Right hemiplegia, somnolent, aphasic. Pilledema. Arteriovenous anomaly of left middle cerebral artery—by angiography.	Craniotomy—intracerebral clot and anomaly removed.	Not stated.	Patient well.

TABLE III. P.—Continued

Author	Case No.	Age Parity	Duration of Pregnancy at Hemorrhage	Neurological Data	Management	Mode of Delivery	Puerperium
Christensen and Larsen (25)	82	27 ?	9 months	Four year history of attacks of pain. Paresthesiae beginning in right hand and radiating into right trunk and leg. Left carotid angiogram—aneurysm of parietal region. X-ray therapy. Sudden coma, died in 4 hours. Post mortem—rupture of arteriovenous aneurysm and presence of thick-walled thrombotic aneurysm.	—	—	—
Conley and Rand (5)	83	30 multi-para	5½ months	Suddenly "dizzy," felt ill, complained of severe headache, and died. Post mortem—rupture of arteriovenous malformation of cerebellum.	—	—	—
Christensen and Larsen (25)	84	24 ?	8 months	One year previously, headache, stiff neck, paresis of left hand. Sudden paresthesiae and paralysis of right arm, then paresthesiae and paralysis of legs, followed by paresis of left arm, stiff neck.	Supportive.	Forceps delivery, dead baby.	Died in 2 days. Post mortem—hemangioma of cervical medulla with hemorrhage into medulla.

Sullivan, Campbell, and Gra- ham (29)	85	23 0	9 months	Sudden head pain, right eye ptosis, then coma and respiratory paralysis in one hour.	Supportive.	Cesarean section—nor- mal baby.	Did poorly and died in 45 hours. Post mor- tem—right tempora- lobe intracerebral he- matoma at base of which was “a tangle of vessels”—arterio- venous anomaly.
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rhages at nine, eight, eight, and five months of pregnancy, respectively, delivered normally. The diagnosis of vascular anomaly was made after delivery in Cases #12 and #76. The former patient has been reported in detail and, as of 1955, has had about thirty-five episodes of subarachnoid hemorrhage, the last two occurring in spite of carotid artery ligation. Patients #13 and #77 had angiography while pregnant and delivered at term uneventfully.

ii. Patient #78 had one hemorrhage in each of two pregnancies, occurring within the first five months of pregnancy. Delivery each time was by cesarean section. Nine months after the last hemorrhage, she underwent neurosurgery. She had two additional craniotomies and died following the last operation.

iii. Patients #79 and #80 bled at four and a half and four months respectively. Both had successful craniotomies and subsequently were allowed to deliver vaginally. However, patient #79 was sterilized.

iv. Patient #81 had an anomaly of the left middle cerebral artery which was successfully excised after it bled in the seventh month of pregnancy. The mode of delivery was not stated.

v. The remaining four patients (#82, #83, #84, #85) suffered fatal intracranial hemorrhages at, respectively, nine, five and a half, eight, and nine months of pregnancy. One baby (#85) was saved by emergency cesarean section. Patients #82 and #85 were unusual. The former had both a large aneurysm and a large arteriovenous malformation which ruptured and caused her demise. The aneurysm at post mortem had an intact, thick thrombotic wall. Patient #85 had a hemangioma of the upper cervical spinal cord which bled into the parenchyma of the spinal cord and lower medulla.

Thus, excluding the patients who were admitted in a terminal state, one patient had a cesarean section and six were delivered vaginally—two after surgery. Neurosurgery is not essential and actually is a most controversial subject with respect to arteriovenous malformations in the brain. This cannot be evaluated in this paper. However, one of the three patients in this group apparently died after her third craniotomy. The patient who had a carotid artery ligation bled twice after surgery. It does seem feasible to deliver vaginally those patients who bleed from vascular anomalies during pregnancy.

C. The thirty-seven patients with subarachnoid hemorrhage of unknown cause (#14, #15 and Table III.C) naturally had very little intracranial surgery.

i. Eleven patients (#15, #86, #87, #88, #89, #90, #91, #92, #93, #94, #95) delivered vaginally. They had intracranial hemorrhages, respectively, at nine, four, nine, two and a half, six, six, three and a half, seven, seven and a half, unknown, and unknown months of pregnancy. Patient #15 was not diagnosed as having subarachnoid hemorrhage until the fourth day postpartum, when the cerebrospinal fluid was found to be xanthochromic. She has expressed a great deal of unhappiness at having been advised against further pregnancies. Patients #86, #87, and perhaps #93, had two episodes of intracranial hemorrhage. Only #87 had her recurrence while pregnant. Patient #86 hemorrhaged the third time four years after the birth of her baby. Both patients #86 and #87 had angiograms, neither of which was positive for an

aneurysm or arteriovenous anomaly. Patient #95 subsequently had another normal pregnancy and again delivered uneventfully by the vaginal route.

Patient #110 bled in the sixth month of pregnancy and, in spite of normal angiography, had a craniotomy and decompression followed by ligation of the internal carotid artery. At term, she was allowed to deliver vaginally.

ii. Patient #14 suffered intracranial hemorrhage at three months of pregnancy but had a spontaneous miscarriage in her fifth month.

iii. Patient #96 had an intracranial hemorrhage at four and a half months, and then a therapeutic abortion.

iv. Patient #97 suffered from placenta praevia and, with the onset of vaginal bleeding, she also developed intracranial hemorrhage. Cesarean section was performed for obstetrical reasons under spinal anesthesia. The lumbar puncture revealed bloody fluid.

v. Twelve patients (#98, #99, #100, #101, #102, #103, #104, #105, #106, #107, #108, #109) had intracranial hemorrhage but were delivered by cesarean section. They suffered intracranial hemorrhage, respectively, at two, four, six and a half, two, three, five, seven, eight and a half, eight and a half, eight and a half, nine, and nine months of pregnancy. During pregnancy patient #100 had one recurrent intracranial hemorrhage, and patient #105 had two episodes of recurrent hemorrhage. Normal angiograms were noted in patients #99, #106 and #107. Patients #101, #102 and #106 had tubal ligations; patient #108 was advised against further pregnancy. Patient #106 was admitted in coma, eight and a half months pregnant, and had a cesarean section followed by tubal ligation. Following delivery bilateral carotid angiography demonstrated a temporal lobe mass. Craniotomy was performed, an intracerebral clot was removed, and she improved. No source of bleeding was demonstrated by angiography or was seen at surgery.

vi. Ten patients (#111, #112, #113, #114, #115, #116, #117, #118, #119, #120) had sudden fatal intracranial hemorrhages. They bled, respectively, at five, eight, eight, nine, third trimester, nine, eight, seven, six and a half, and eight and a half months of pregnancy. Patient #17 had had an intracranial hemorrhage while pregnant three years previously. Patient #111 had a blood pressure of 240/190. The babies of three moribund patients (#113, #114, #120) were saved by cesarean section. Most significantly, patients #115, #116, #117, #118, #119 and #120 had post mortem examinations in which no aneurysms or arteriovenous anomalies were found. Patient #117 had "a rupture of a branch of the anterior cerebral artery." Patient #120 had had a "lesion" of the right middle cerebral artery.

In this group there was no significant clinical difference in the eleven patients who delivered vaginally and twelve who had cesarean sections. Five of the latter cases (#105, #106, #107, #108, #109) hemorrhaged close to term and management would tend to follow the statement in the literature "in cases of recent hemorrhage (within three weeks) cesarean section may occasionally be indicated" (21). None of the eleven patients delivered vaginally had any intracranial complication during labor or in the puerperium.

These patients also underscore the fallacy of assuming that subarachnoid

TABLE III.C
Spontaneous Subarachnoid Hemorrhage (Bleeding due to "Torn" Artery or "Cause Unknown")

Author	Case No.	Age Parity	Duration of Pregnancy at Hemorrhage	Neurological Data	Management	Mode of Delivery	Puerperium
Camell and Botterell (2)	86	30 1	4 months	This was second episode of hemorrhage.	None stated.	Normal delivery.	Four years after birth, she had a third subarachnoid hemorrhage. Left carotid angiogram was normal.
Christensen and Larsen (25)	87	24 2	9 months	Sudden unconsciousness, stiff neck. Did well. Twenty days later, recurrent hemorrhage. Again recovered.	Supportive.	Spontaneous delivery 3 days after last hemorrhage.	Normal. Angiography six weeks later—"dubious left-sided findings." Right carotid angiogram normal.
Millen (30)	88	35 multi-para	2-3 months	Not stated.	Supportive.	Spontaneous delivery.	Normal.
Conley and Rand (5)	89	21 ?	6 months	Headache, vomiting, positive Kernig sign.	Supportive.	Spontaneous delivery; low forceps baby, live.	Normal. Slight left rec-tus weakness.
Finola (31)	90	21 1	6 months	Stiff neck, lethargy, right hemiparesis.	Supportive.	Normal delivery under cyclopropane with outlet forceps.	Normal.
	91	41 5	3½ months	Coma, convulsions, right hemimotor-sensory syndrome.	Supportive.	Normal delivery under cyclopropane.	Normal.
Flening and Mauzy (32)	92	30 1	7 months	Headache, nuchal rigidity?	Supportive	Normal delivery with saddle block and low forceps.	Normal.
Walton (21)	93	35 0	7½ months	Sudden head pain and convulsion, stiff neck. Six years ago, headache—diagnosis "meningitis."	Supportive.	Spontaneous normal delivery.	Normal.

Lautstein, Koitz, and Hehre (6)	94	24	?	Not stated.	Supportive.	Vaginal delivery with cyclopropane, live baby.	Normal.
	95	22 1	?	Not stated.	Supportive.	Vaginal delivery with- out anesthesia, live baby.	Normal. Two subse- quent pregnancies, one an ectopic and the last a normal de- livery with cyclopro- pane.
Gomberg (11)	96	22 1	4½ months	None stated. Angiog- raphy?	Supportive.	Therapeutic abortion.	—
Garber and Maier (33)	97	26 0	8 months	Vaginal bleeding (pla- centa praevia?). Headache and vomit- ing with onset of va- ginal bleeding, stiff neck, positive Kernig sign.	Supportive.	Cesarean section due to placenta praevia. Spinal tap for anes- thesia revealed bloody fluid.	Normal.
Mack, Schreiber, Niel- sen, and Huber (7)	98	33 multi- para	2 months	Sudden headache and senicoma, nystag- mus on right lateral gaze with diplopia, inability to look up. Arteriography—nor- mal.	Supportive.	Cesarean section.	Normal.
Daane and Tandy (9)	99	18 0	4 months	Sudden "indescribable feeling" in right ex- tremities, hemiple- gia, aphasia, coma. Slow, gradual im- provement. Angio- gram—no abnormal- ity.	Supportive.	Elective low cesarean under local anesthe- sia, live baby.	Normal.

TABLE III.C—Continued

Author	Case No.	Age-Parity	Duration of Pregnancy at Hemorrhage	Neurological Data	Management	Mode of Delivery	Puerperium
Mack, Schreiber, Nielsen, and Huber (7)	100	23 0	6½ months	Sudden severe headache, stiff neck, mental confusion, semi-comatose. Rectum covered partially—hemiparesis; 4 weeks later, severe headache, stiff neck.	Supportive.	Elective low cesarean section under local anesthesia with penicillin, live baby.	Normal.
	101	26 1	2 months	Headache, vomiting, right eye ptosis, facial palsy.	Supportive.	Cesarean section under spinal anesthesia. Elective tubal ligation.	Normal.
	102	35 4	3 months	Not stated. Angiography?	Supportive.	Cesarean section and tubal ligation.	Normal.
Johnson (34)	103	36 1	5 months	Sudden headache, vomiting, double vision, stiff neck, lethargy.	Supportive.	Cesarean section.	Not stated—apparently did well.
Conley and Rand (5)	104	32 0	7 months	Sudden severe headache.	Supportive.	Cesarean section at term.	Normal.
Garber and Maier (33)	105	26 multi-para	8½ months	Sudden severe headache and vomiting. Papilledema. Stiff neck. Seven days later, 2nd hemorrhage; 23 days after first attack, third hemorrhage with unconsciousness, then organic psychoses. Two days later, moribund.	Supportive	Cesarean section under spinal anesthesia, live baby.	In spite of critical state, she eventually did well.

Gomberg (11)	106	31 1	8½ months	Comatosed.		Cesarean section 12 hours after admis- sion followed by tu- bal ligation.
Robb (35)	107	34	8½ months	Following delivery, bi- lateral carotid angi- ography—left ten- poral lobe mass. No aneurysm. Headache, dysphasia, right facial weak- ness, stiff neck.	Craniotomy—with de- compression after re- moval of mass of clotted blood. Grad- ually improved. Supportive.	Cesarean section. Normal. Followed by left carotid angio- gram—normal.
Rand (36)	108	26 multi- para	9 months	Sudden headache, bi- lateral positive Ker- ning sign.	Supportive.	Cesarean section, live baby. Normal. Advised against pregnancy.
Copelan and Mabon (18)	109	41 4	9 months	Sudden head pain, vomiting.	Supportive.	Low cervical cesarean section under cyclo- propane. Live baby.
Pedowitz and Perell (37)	110	21 3	6 months	In coma with convul- sions. Angiography —normal.	Craniotomy and de- compression, then internal carotid ar- tery ligation. Supportive.	Delivered spontane- ously a full term baby. Normal.
Jarvinen and Hulmar (38)	111	32 1	5 months	Found unconscious at home, admitted in coma, left-sided re- flexes spastic. Blood pressure 240/190. Died without regain- ing consciousness. No autopsy.		—
Pedowitz and Perell (37)	112	27 0	8 months	In coma with convul- sions. Died 45 min- utes after admission. No post mortem.	Supportive.	Post mortem cesarean section—baby died, also.

TABLE III.C—*Continued*

Author	Case No.	Age Parity	Duration of Pregnancy at Hemorrhage	Neurological Data	Management	Mode of Delivery	Puerperium
Bleakney (14)	113	35 0	8 months	Sudden headache, numbness of right face, tongue, upper extremity. Comatosed in 6 hours. Sudden coma.	Supportive.	Cesarean section—live baby.	Patient died 3 hours after admission.
Ramstad (39)	114	37 0	9 months	Treated for syphilis nine years previously. Sudden headache, vomited; convulsions—died. Post mortem—no source of hemorrhage.	Supportive.	Cesarean section—live child.	Died immediately after section. No post mortem.
Paucot and Gelle (40)	115	43 13	In the last trimester	Sudden unconsciousness and convulsions, comatosed, died in 4 hours. Post mortem—right frontal intracerebral hematoma. No site of hemorrhage. Incidental pituitary chromophobe adenoma.	Supportive.	Post mortem cesarean section—dead baby.	—
Christensen and Larsen (25)	116	26 ?	9 months	Neck pain, vomiting, unconscious six days. Papilledema. Died. Post mortem—rupture of branch of anterior cerebral artery.	Supportive.	Post mortem cesarean section—stillborn.	—
Masten (41)	117	22 ?	8 months				

Gomberg (11)	118	27 1	7 months	(A previous hemorrhage late in pregnancy occurred three years prior.) Headache, stiff neck. Two weeks later, convulsion and death. Post mortem—hemorrhage into right fronto-parietal area and ventricle. No source of hemorrhage.	Not stated. Supportive.	Not stated. —	Not stated.
Schwartz (19)	119	24 0	6½ months	Well prior to being found unconscious at home. Died within two hours after hospitalization. Post mortem—subarachnoid hemorrhage, cause undetermined. Sudden headache, convulsion, bilateral Babinski—comatosed.	Supportive.	Post mortem cesarean section—baby died.	—
Hassett (42)	120	37 3	8½ months		Supportive.	Attempt at vaginal delivery—5 U.S.P. units of pitocin added to infusion. Eight hours later because of “unproductive” contraction, cesarean section, live baby.	Given ergotrate 4 hours after section. Died within 24 hours. Post mortem—“lesion” of right middle cerebral artery.

hemorrhage is invariably due to aneurysm. Six patients had autopsies and no congenital anomaly was noted. Six additional patients had normal angiograms (total angiography was not stated).

Considering the additional risk of cesarean section, it seems clear that in subarachnoid hemorrhage of unknown cause delivery can be by the vaginal route.

SPONTANEOUS SUBARACHNOID HEMORRHAGE DURING LABOR
OR THE IMMEDIATE POSTPARTUM PERIOD
(FIRST TWENTY-FOUR HOURS)

The recommendation of cesarean section for the pregnant patient who has had intracranial hemorrhage is based on studies implying additional strain on the cerebral vasculature. Marx, Zemaitis and Orkin (44) state that during the second stage of labor, the average increase in cerebral spinal fluid pressure is 710 mm of fluid above normal. Adams (45) reported that the cardiac output begins to rise by the end of the third month, reaches its peak about the twenty-eighth week of pregnancy (32% increase from pre-pregnancy base line), then falls to "normal" levels by forty weeks of pregnancy. Abrupt strain on the cardiovascular system with abrupt (25%) increase in cardiac output occurs during the first hour after delivery. This is maintained until about the sixth postpartum day. Adams and Alexander (46) also noted that cardiac output increased 20 per cent during a single uterine contraction. The mean blood pressure increased from 116/76 to a mean of 127/82 at the height of contraction. McClausland and Holmes (47) state that intraspinal (intracerebral?) pressures during uterine contractions with the patient bearing down vary from 240 to 700 mm of fluid. During regular contractions, spinal fluid pressure usually showed only minimal rise.

Nevertheless, the clinical data does not confirm the reputed "extra strain" of labor.

There were no patients at this institution who developed intracranial hemorrhage in labor or the immediate twenty-four hour postpartum period. However, in the literature (Table IV) twenty-seven such cases are reported.

i. No patient suffered a rupture of an intracranial aneurysm during labor. It has been estimated that the incidence of intracranial aneurysms in the population is from 0.5% to 1% (52). On the basis of four million deliveries a year, approximately 20,000 to 40,000 women who deliver annually may also have an intracranial aneurysm. One may hypothesize that in the past two decades approximately a half million such patients delivered and it is amazing that not one case has ever been reported to the best of the author's knowledge. In addition to this statistical incidence, many patients have given birth to children without difficulty and later in life suffered intracranial hemorrhage proven to be due to aneurysms. It has been previously noted in this study that aneurysms which have bled do not necessarily re-bleed during labor (patients #2, #20, #21, #22).

Actually, Magee (56) in studying nonpregnant patients who developed sub-

arachnoid hemorrhage found that 90 per cent of his patients bled when they were undergoing no physical strain. He believed that physical stress in general has not been well correlated to the actual rupture of a blood vessel anomaly.

One may only conclude that the fear of rupture of an aneurysm in labor is a theory not confirmed by clinical experience.

When the potential problems of major abdominal surgery entailed by cesarean section are weighed against an unsubstantiated fear (plus the clinical experience that a section does not prevent intracranial bleeding—patients #48, #50, #51), vaginal delivery seems to be preferable.

The question of anesthesia has not been mentioned in this study. The clinical data available does not allow critical evaluation of the various ways of administering anesthesia. A continuous technique of extradural block seems to be preferable in vaginal delivery (6). The judicious use of forceps can also shorten the second stage of labor.

ii. Patient #121 had an arteriovenous anomaly which may have bled in labor. An unusual amount of headache occurred immediately after birth. She definitely hemorrhaged four days later and angiography demonstrated the lesion. However, it has already been noted that six patients with vascular anomalies went through labor without an intracranial complication.

iii. Twenty patients bled during labor or within the immediate twenty-four hour postpartum period, and no aneurysms or arteriovenous anomalies were demonstrated.

Patients #122, #123 and #124 had angiograms which were normal. Patient #122 had an intracranial hemorrhage during labor. The other two had hemorrhaged seven and four hours after delivery.

Patient #125 began to convulse in labor. After delivery she underwent a craniotomy for evacuation of an intracerebral hematoma. No source of bleeding was seen. Angiography was not performed.

Seven patients (#126, #127, #128, #129, #130, #131, #132) died and were autopsied. Patient #126 was most unusual because she had an incidental pheochromocytoma and, after intramuscular ergotrate, her blood pressure rose. The site of bleeding could not be determined. None of these eleven cases had an aneurysm or malformation on post mortem examination.

The remaining nine patients were undiagnosed. Patients #133, #134, #135 and #136 survived, but did not have angiography. Five fatal cases (#137, #138, #139, #140, #141) did not have autopsies. Patient #133 apparently bled three times during the postpartum period before she succumbed. The various authors reporting these cases detailed the drugs, such as pitocin and ergotrate, which were administered. However, since these drugs are given routinely by most obstetricians, it is stretching a point to attempt to infer causal relationship. One would imagine that if such a situation existed, there would be many more cases of subarachnoid hemorrhage in labor. Some of these patients who did bleed may have had an idiosyncratic reaction to the drugs.

iv. Six patients had cesarean sections. Patients #142 and #143 had elective obstetrical procedures and did not have any labor experiences. Patient

TABLE IV
Spontaneous Subarachnoid Hemorrhage Occurring During Labor or in the Immediate Postpartum Period

Author	Case No.	Age Parity	Mode of Delivery	Clinical Course	Management	Puerperium
Conley and Rand (5)	121	29 0	Spontaneous delivery.	Unusual amount of headache immediately postpartum.	Supportive.	Four days later, stiff neck. Four days thereafter, motor aphasia and right facial weakness. Carotid angiogram—large anomalous vein in arterial phase. Did well thereafter.
	122	34 3	Spontaneous delivery.	In labor, complained of headache and vomiting. Generalized seizure after birth of baby. Neck stiff, bilateral Babinski.	Bilateral carotid and vertebral angiography—all normal.	Stormy, but did well.
	123	26 1	Spontaneous delivery.	Spontaneous delivery with low forceps. 1/320 grain ergotrate given after birth of baby and repeated twice in six hours. Seven hours after delivery, convulsion beginning in left wrist, recurred but had left hemiplegia.	Supportive. Right carotid angiogram—normal.	Normal.
Cannell and Botterell (2)	124	27 2	Pitocin induced for postmaturity—normal baby.	4 hours after delivery developed a subarachnoid hemorrhage.	Supportive.	Angiography—normal. No further pregnancy.
Hall and Corradini (48)	125	25 0	Spontaneous delivery.	Blood pressure 108/70. In labor, right hand and arm twitched, then left-sided convulsion.	Craniotomy—intracerebral hematoma left frontal area. Source of bleeding unknown.	Not stated.

Mack, Schreiber, Nielsen, and Huber (7)	126	30 multi-para	Outlet forceps.	Rapid labor, delivered by outlet forceps under spinal anesthesia; at third stage, 1 cc ergotrate I.M., blood pressure rose from 135/80 to 148/110, headache, stiff neck, hemiplegia, coma—death. Second stage of labor 2 hours. "Patient appeared unusually sedated for the small amount of medication given." At end of episiotomy repair, convulsion ensued. Blood pressure 138/90. One hour later, decerebrate rigidity. Three hours later, blood pressure 180/110, convulsion, coma, and death in three days.	Supportive.	Post mortem—intracranial hemorrhage, no site of bleeding noted; she also had a pheochromocytoma (assay—1 Gm epinephrine).
Copelan and Mabon (18)	127	31 0	Normal prenatal course. Baby delivered by "difficult forceps rotation."	"Patient appeared unusually sedated for the small amount of medication given." At end of episiotomy repair, convulsion ensued. Blood pressure 138/90. One hour later, decerebrate rigidity. Three hours later, blood pressure 180/110, convulsion, coma, and death in three days.	Supportive.	Died in 30 hours. Post mortem—rupture of left middle cerebral artery; "possibly at the site of congenital aneurysm."
Lazard (49)	129	22 0	Normal prenatal course and delivery.	Three hours later, blood pressure 180/110, convulsion, coma, and death in three days.	Supportive.	Post mortem—subarachnoid hemorrhage, no site of bleeding. "The multiple petechiae so often seen in eclampsia were not found."
Gomberg (41)	130	27 0	Normal labor. Spontaneous delivery.	After 12 hours labor, 6-month fetus delivered. As placenta was being extracted, patient became stuporous and had a convulsion beginning in right hand. One hour after delivery, headache, vomited. Four hours later, convulsion, then coma, with right hemiparesis.	Supportive.	Died in 12 hours. Post mortem—left frontoparietal hemorrhage. No source of bleeding.

TABLE IV—*Continued*

Author	Case No.	Age Parity	Mode of Delivery	Clinical Course	Management	Puerperium
Moskowitz and Schneider (50)	131	25 0	Normal labor. Undelivered.	"Syncopeal episode" in last trimester of pregnancy. After 7 hours labor, sudden headache and "dizziness;" 25 minutes later, comatosed and death 5 minutes thereafter.	Supportive.	Post mortem—cerebral hemorrhage, cause undetermined.
Conley and Rand (5)	132	33 multipara	Spontaneous delivery.	Convulsion just prior to onset of labor. Spontaneous delivery under spinal anesthesia. Severe headache immediately after delivery with rapid development of decerebrate rigidity and coma.	Supportive.	Death in 6 hours. Post mortem—no source of hemorrhage.
Cannell and Botterell (2)	133	40 8	Spontaneous—normal baby.	Two hours after delivery, some headaches.	Supportive.	Three attacks of intracranial bleeding within a few days of delivery. Improved. Denied angiography.
Stevens (51)	134	29 1	Spontaneous—normal baby.	Five and one half hours after delivery, drowsy and left hemiplegia. Slight nuchal rigidity.	Supportive.	
Moskowitz and Schneider (50)	135	26 2	Spontaneous delivery.	Spontaneous delivery, 6 hours labor. One half cc pituitrin following birth of baby, 1 cc ergobasine subsequent to delivery of placenta. Two hours after delivery, headache, vomiting, "dizziness;" in stupor next day. Neck stiff.	Supportive.	Normal.

Hall and Corradini (48)	137	?	?	Spontaneous delivery.	headache before labor. Six hours postpartum, convulsions and then coma. Blood pressure 158/90. Lethargy and right hemiparesis during second stage of labor.	Supportive.	Died 48 hours postpartum. No autopsy.
Järvinen and Huhner (38)	138	33 4	33 4	Normal delivery.	(Albuminuria on admission.) Normal delivery of twins. Three hours after delivery, headache, vomited, and lapsed into coma.	Supportive.	Died in 24 hours. No autopsy.
Chesley (53)	139	25 0	25 0	Low forceps under spinal anesthesia—live baby.	Admitted in labor. Blood pressure 122/78. Four hours thereafter, left leg weak, left hemiparesis, left Babinski. (Pre-eclampsic?) Pituitrin and gynergen, 1 cc each, were given after 13 hours labor. Ten minutes after delivery of placenta, sudden coma.	Supportive.	Patient comatosed after delivery. Developed convulsions. Died in 63 hours. No autopsy.
Moskowitz and Schneider (50)	140	25 0	25 0	Spontaneous delivery.		Supportive.	Died 6 hours later. No autopsy.
Mack, Schreiber, Nielsen, and Huber (7)	141	32 multi-para	32 multi-para	Induced labor.	After castor oil and quinine, induction with 2-3 minims doses of pituitary extract. Rapid exitus after second dose with signs of massive intraerantal hemorrhage.	Supportive.	No autopsy.
Copelan and Mabon (18)	142	25 1	25 1	Low cervical cesarean section under spinal anesthesia (elective—previous cesarean section three years earlier for inertia).	Chronic alcoholic with admission 9 days prior to delivery for acute alcoholic intoxication. Patient complained of headache after spinal injection, became restless during operation requiring general anesthesia. At end of procedure, developed spastic movements of all extremities, was unconscious. Four hours later, aphasic.	Supportively given hypothermia, Levophed, and cortisone.	Died 30 hours later. Post mortem denied.

TABLE IV—Continued

Author	Case No.	Age Parity	Mode of Delivery	Clinical Course	Management	Puerperium
Smolik, Nash, and Clawson (15)	143	28 1	Cesarean section due to previous placenta praevia—under spinal anesthesia.	Ergotrate given into uterine musculature. Sudden severe headache, convulsion, decerebrate rigidity.	Right carotid angiogram—downward displacement of middle cerebral artery. Ventriculogram—right-sided mass lesion. Craniotomy—evacuation of intracerebral hematoma.	Patient died next day. Post mortem—bleeding due to "torn middle cerebral artery."
Weigle (54)	144	22 0	Vaginal delivery attempted. But, after 15 hours without progress and patient semicomatose, cesarean section done—live baby. Also bilateral tubal ligation.	Patient had bacterial endocarditis and was being treated with penicillin and cyclocumaryl. Developed headache and vomiting.	Supportive.	Died 24 hours later. Post mortem—confirmed endocarditis. Also extradural hematoma around base of sella turcica.
Mack, Schreiber, Nielsen, and Huber (7)	145	22 0	Cesarean section.	Mild eclampsia, cesarean section under spinal anesthesia after induction of labor with pituitary extract had failed. Blood pressure 150/80 at surgery. With spinal anesthesia, given vasopressor drug. Pituitary extract given after placenta removed. After surgery, 1 cc ergotrate intravenously to counteract atonic uterine bleeding. Sudden headache, blood pressure 230/110, coma.	Supportive.	Died in 23 hours. Post mortem—brain stem hemorrhage.

Conley and Rand (5)	146	26 1	Cesarean section—live baby.	During labor, sudden severe headache, neck rigid, posi- tive Kernig sign bilater- ally. Cesarean recom- mended.	Supportive.	Normal. Advised against future pregnancies, but had another baby 6 years later. Patient also listed as #33.
Millen (30)	147	45 0	Cesarean section.	Cesarean section because of no progress after 16 hours of ruptured membranes and 12 hours labor. Several hours later, sudden spastic right-sided paralysis.	Supportive.	Stormy course, but did well.

№142 developed neurological symptoms concomitant with spinal anesthesia. Post mortem permission was denied. Patient №143 developed a neurological syndrome following ergotrate. She had an autopsy and there was "a torn middle cerebral artery." Patients №144, №145, №146 and №147 all had a trial of labor. Patient №144 suffered from subacute bacterial endocarditis. She died twenty-four hours after surgery. No mycotic aneurysm was found, but there was marked bleeding around the sella turcica. Patient №145 was a pre-eclamptic. Introduction of labor with pituitary extract failed and a cesarean section was then performed. With the spinal anesthesia she was given a vasopressor drug. Pituitary extract was given after the placenta was delivered. One cubic centimeter of ergotrate was administered intravenously to counteract atonic uterine bleeding. She developed a sudden headache, her blood pressure rose to 230/110, and she became comatose. An autopsy revealed a brain stem hemorrhage but no aneurysm or arteriovenous anomaly. Patient №146 was in labor when she developed intracranial bleeding. Cesarean section was immediately recommended. She did well, but angiography was not done. Although advised against future pregnancies, she became pregnant again. She appears earlier in this study as patient №33.

Among these twenty-seven patients only one had a congenital lesion (№121 had an arteriovenous malformation). The frequently stated assumption that labor resulted in the rupture of an intracranial aneurysm could not be proven in ten post mortem examinations. There were torn blood vessels noted but no aneurysms or anomalies. Three additional patients had normal angiograms (№133 had total angiography), and one patient had a craniotomy during which no abnormal vessel was encountered.

Moreover, following cesarean section in four patients (two had elective surgery, two had nonproductive labor) subarachnoid hemorrhage occurred.

The above clinical data does not prove that labor has any special untoward effect on congenital intracranial lesions—either aneurysms or anomalies. Neither does a cesarean section give any special extra protection against intracranial hemorrhage.

SPONTANEOUS SUBARACHNOID HEMORRHAGE IN THE PUERPERIUM

There were four patients who delivered babies at this institution and then suffered intracranial hemorrhage in the puerperium. Their clinical data is detailed below:

16. I.K., age 36, para 1. At age 35, when she was 25 weeks pregnant, she had a spontaneous abortion ("twin pregnancy" with two previous admissions—at 3½ and 5 months—because of incipient miscarriage). On the fourth postpartum day, there was a sudden onset of severe head pain, vomiting and photophobia. There was tingling in the left foot just before and at the onset of severe headache. The neurological examination was normal, except for a stiff neck. The next day, she developed an organic mental syndrome, a left homonymous hemichromatopsia, a dilated left pupil, and a left facial weakness. Bilateral carotid angiography failed to show the source of bleeding. She has

done well and has been advised that there is no contraindication with respect to future pregnancies.

17. M.K., age 27, para 3. At age 24, on the fourth postpartum day, after spontaneously delivering her third child, she developed severe head pain. Within twenty-four hours, a severe organic mental syndrome developed. During the initial neurological examination, a grand mal convulsion ensued. There was no focal onset. There were no focal neurological findings at any time. In spite of high doses of anticonvulsants, grand mal seizures occurred three to four times over the next three days. Bilateral carotid and vertebral angiography were all normal. The seizures were controlled and she has done well. Future pregnancies have been disadvised.

18. S.K., age 36, para 0. At age 26, three weeks following a spontaneous delivery, she suffered a sudden onset of loss of power of speech. Grand mal seizure ensued. Upon regaining consciousness, she complained of severe headache. There was minimal right-sided weakness. Left carotid angiography demonstrated elevation of the middle cerebral artery indicative of a mass in the temporal lobe. She was treated supportively and did well. She has been cautioned against future pregnancies. There has been no recurrence of intracranial bleeding.

19. E.G., age 24, para 1. This young woman delivered a normal child without difficulty under general anesthesia. Low forceps were used. She was well and asymptomatic when discharged on the fifth hospital day. On the sixth day postpartum, she was found dead in bed. The body was taken to the hospital and a post mortem examination was done. Diagnosis: subarachnoid hemorrhage, source of bleeding unknown. There were no aneurysms or vascular anomalies.

In the literature (Table V), twenty-five additional cases are reported—three had aneurysms, four had venous thromboses, and fourteen had no determined cause of hemorrhage.

i. It is most difficult to blame labor for the intracranial bleeding in the three aneurysm cases. Patient #148 did not hemorrhage until the fourth postpartum day. It is noteworthy, however, that she was given ergotrate the evening before the intracranial hemorrhage because of vaginal bleeding. Patient #149 had a therapeutic abortion for malignant hypertension and bled fatally five days later. Patient #150 had a mycotic aneurysm secondary to subacute bacterial endocarditis, which was a complication of a septic abortion.

ii. Among the eighteen patients whose source of bleeding was undetermined, three (#16, #17, #18) had normal angiograms. Patient #17 had visualization of the entire cerebral vasculature. Patient #19 was found dead in bed five days after delivery. A post mortem did not reveal either an aneurysm or an arteriovenous anomaly. Patient #151 had a subarachnoid hemorrhage apparently secondary to occlusion of an internal carotid artery. Patient #152 had a cesarean section for renal disease, became comatose on the seventh postpartum day, and died. An autopsy revealed no congenital malformation.

Ten (#153, #154, #155, #156, #157, #158, #159, #160, #161, #162) of the remaining patients did well. They bled, respectively, on the thirteenth,

TABLE V
Spontaneous Subarachnoid Hemorrhage in the Puerperium

Author	Case No.	Age Parity	Mode of Delivery	Postpartum Day of Onset of Neurological Illness	Neurological Data	Management
Speck (57)	148	35 1	Spontaneous delivery.	4	Passed several clots; given ergo- trate grains $\frac{1}{320}$ t.i.d. p.o.; that evening, severe occip- ital headache, nausea, vomit- ing. Next morning, drowsy and stiff neck.	Six days later, angiogram re- vealed aneurysm at origin of posterior communicating ar- tery. Right common carotid artery ligation.
Gomberg (11)	149	34 ?	? gestation period—malignant hypertension, therapeutic abortion.	5	Sudden death. Post mortem— rupture basilar artery aneu- rysm.	—
Cannell and Botterell (2)	150	?	Septic abortion complicated by subacute bacterial endocar- ditis.	?	Subarachnoid hemorrhage from a mycotic aneurysm of basilar artery.	
Trodella (58)	151	23 0	Normal delivery under spinal anesthesia with low forceps.	3	Convulsion and had status epi- lepticus, gradually improved.	Supportive. Bilateral carotid angiography—occlusion of right internal carotid artery. Died well.
Boshes and McBeath (8)	152	29 2	Cesarean section because of renal disease.	7	Comatosed—left hemiparesis. Bilateral carotid angiography —? defect.	Right carotid artery ligation. Died 28 hours after surgery. Post mortem—no deter- mined cause of bleeding. Supportive. Died well.
Flexner and Schneider (59)	153	20 0	Low forceps normal delivery.	13	Developed urticaria. Next day given 5 cc of $\frac{1}{1000}$ epineph- rine. Forty-five minutes there- after, severe headache, vom- ited, stiff neck, Kernig sign.	
Gershenfeld and Savel (60)	154	24 0	Spontaneous delivery.	3	Complained of headache. Ther- apy—ergostrate $\frac{1}{320}$ grain I.M.; icebag and caffeine so- dium benzoate. Fourth day— lethargic, stiff neck, positive Kernig sign.	Supportive. Three-month fol- low-up normal.

Johnson (34)	155	26 1	Spontaneous delivery, low forceps.	8	Severe headache, confusion, stiff neck, right Babinski sign.	Supportive. Did well.
Garber and Maier (33)	156	24 0	Spontaneous delivery, low forceps.	2	Marked headache followed by stiff neck, positive Babinski.	Supportive. Did well.
Järvinen and Huhner (38)	157	26 1	Normal delivery.	1-2	Headache before and after delivery. 1 day postpartum—poor vision; 2 days postpartum—stiff neck, positive Kernig sign.	Supportive. Did well.
King (61)	158	20 0	Normal delivery.	1	Sudden right hemiplegia. Developed papilledema.	Ventriculogram—no abnormalities. Discharged; one year later, convulsions began. Supportive. Did well.
Martin (62)	159	40 8	Normal delivery.	17	Convulsion, right hemiparesis, right Babinski sign.	Supportive. Not stated but apparently did well.
Rhoads (20)	160	27 2	Normal delivery.	9	Had a convulsion—onset in right hand.	Supportive. Did well.
Cairns and Melton (63)	161	29 2	Not stated.	17	Three days severe vaginal hemorrhage requiring on 14th postpartum day a blood transfusion. No abnormal reaction. 17th postpartum day, convulsions, headache. Postictal state—astereognosis of left hand.	Supportive.
Copelan and Mabon (18)	162	27 0	Low cervical cesarean section due to 10 hours labor and fetal distress.	6	Sudden headache and stiff neck. Slight decrease in deep reflexes of left arm. Four days later, speech difficulty, left facial paralysis, numbness of left arm lasting 5 minutes. Two hours later, similar attack but weakness of right arm.	

TABLE V—Continued

Author	Case No.	Age Parity	Mode of Delivery	Postpartum Day of Onset of Neurological Illness	Neurological Data	Management
Bell (22)	163	36 2	Spontaneous delivery.	3	Had been subject to "head-aches." Following delivery, headaches for two days. Third day, sudden unconsciousness, left hemiparesis, right-sided rigidity, bilateral Babinski signs.	Died quickly. No post mortem.
Ohler and Hurwitz (64)	164	27 ?	Not stated.	17	Sudden confusion, stiff neck.	Patient died. No autopsy.
Martin and Sheehan (65)	165	32 0	Normal delivery.	14	Headache, weakness of left arm, then convulsions. Progressed to hemimotor-sensory syndrome and papilledema.	Craniotomy—thrombosis of right Rolandic vein. Did well post-surgery.
Cannell and Botterell (2)	166	? ?	Normal delivery.	32	No details.	Post mortem—superior sagittal sinus thrombosis.
Hunt (66)	167	21 1	Normal delivery.	20	Sudden severe headache, vomiting, convulsions, aphasia.	Died in 11 days. Post mortem—diffuse hemorrhagic softening with multiple thrombosis of venous system, including sinuses.
Stansfield (67)	168	25 0	Cesarean section.	8	Sudden numbness of right forearm, convulsions, then right hemiplegia.	Supportive. Died in 24 hours. Post mortem—thrombosis superior longitudinal sinus and of veins of left frontal lobe.

third, eighth, second, second, first, seventeenth, ninth, seventeenth, sixth postpartum day. Patient #152 was interesting in that intracranial bleeding occurred forty-five minutes after being given five cubic centimeters of 1/1000 epinephrine for urticaria. Patient #162 had a cesarean section due to ten hours of labor and fetal distress. Patients #163 and #164 bled, respectively, at the third and seventeenth postpartum day. Autopsies were not performed in either case.

iii. There were four patients (#165, #166, #167, #168) who had venous sinus thrombosis in the puerperium. Actually, many other cases of venous sinus thrombosis exist. However, these four were the only ones who clinically presented with proven subarachnoid hemorrhage.

The theory that this condition is somewhat associated with the postpartum increase in blood platelets and plasma fibrinogen has been somewhat weakened by two patients reported, whose thromboses occurred in the first trimester of pregnancy (68). They were not detailed in this study because subarachnoid hemorrhage was not definitely proven. Both these patients developed acute organic mental syndromes with convulsions, stupor, and rapid death.

The postpartum period is only different in that there were patients who suffered from proven sinus thrombosis. However, as noted, this condition can occur in the first trimester of pregnancy as well as in the nonpregnant patient. Again, no correlation existed between congenital lesions such as aneurysms and arteriovenous anomalies causing intracranial hemorrhage and labor. In most instances the latent period between delivery and the episode of intracranial bleeding was such—that if an aneurysm or anomaly ruptured (possible but unproven in patients #153 through #164)—the episode would have to be considered coincidental with the postpartum period.

SUMMARY

An important aspect of this study is the large group of patients whose hemorrhage was undetermined. Ignorance was predominantly due to incomplete angiographic studies which may have been thought to be potentially hazardous to pregnancy. However, potential damage to the fetus by radiation is highest in the first trimester of pregnancy (69). Obviously, angiography may be postponed, if hemorrhage occurs at that time, to a later date when the abdomen can be covered by a lead apron to further diminish any untoward effect. There does not seem to be any report of damage to the fetus by the contrast media and actually this substance is used by obstetricians in determining the position of placenta (70). Although carotid angiography has some morbidity (71), it is very low in the childbearing age group, especially in the absence of intrinsic vascular disease.

In this study, thirty-four patients (twenty with aneurysms, seven with arteriovenous anomalies, and seven with no demonstrable lesions) had diagnostic studies during pregnancy without complications. The new technique of brachial angiography is most effective in obtaining the visualization of the vertebral-basilar circulation. A complete study of the cerebral-vascular tree is

most important in determining prognosis and management of the patient. When the patient's clinical condition permits, these studies should be done. Most likely many of the 96 patients undiagnosed as to the cause of hemorrhage harbored aneurysms or arteriovenous malformations. In this group, 46 patients had no angiography. Twenty-two had procedures but only two had complete visualizations of the cerebral circulation.

There were 25 patients who suffered recurrent hemorrhages. Only two patients who had had intracranial bleeding and subsequently became pregnant suffered any recurrence during the prenatal period, labor or the puerperium. These two (§86—unknown cause; and §12—arteriovenous anomaly) bled prior to, during and after pregnancy—but not in the puerperium. Patient §12 is the one who had thirty-five hemorrhages during her lifetime. Two patients (§78—arteriovenous anomaly; and §117—no congenital lesion at post mortem) bled twice—once in each of two pregnancies. Three patients (§34—arteriovenous anomaly; §38—aneurysm; and §69—aneurysm) had, respectively, three, two, three episodes of hemorrhage prior to pregnancy. Patient §69 succumbed to her fourth hemorrhage in thirteen years during pregnancy. Twelve patients (10—aneurysms; and 2—unknown cause) bled twice during pregnancy: three (§48, §50, §51) bled the second time after cesarean section; three (§64, §65, §66) bled and died before reaching term; three (§54, §59, §60) had neurosurgical procedures after their second episodes of intracranial hemorrhage and then went to term; one (§62) died following neurosurgery. The two without congenital lesions went to term and delivered—one by cesarean section, and one vaginally. Three patients hemorrhaged three times—during pregnancy, §73 who had an aneurysm and was pre-eclamptic, and §105 whose hemorrhage was of unknown cause; during the puerperium, §133 whose bleeding was of unknown cause.

Table VI depicts the months of pregnancy when subarachnoid hemorrhage occurred. Eight patients hemorrhaged in the first trimester, thirty-one in the second trimester, and forty-five in the third trimester. Although, obviously, an increased number of patients hemorrhaged in the last stage of the prenatal period, the total spread over a period of nine months indicates that one cannot per se consider changes in circulation during pregnancy as a primary factor in hemorrhage.

Sixty-six of 168 patients died of subarachnoid hemorrhage. An additional patient who bled twice during pregnancy was operated on and died after surgery. Aneurysms accounted for twenty of 49 patients; arteriovenous anomalies for four of 19; sinus thrombosis for three of 4; unknown cause for thirty of 69 patients. In the last group, post mortem studies were most revealing. Eighteen of 30 patients had autopsies and no congenital lesions were found. This underscores the fallacy of assuming that aneurysm is the usual cause of subarachnoid hemorrhage. Also a frequent soul-searching comment found in literature was to the effect that perhaps an oxytoxic or vasopressor drug contributes to a "weakened congenitally abnormal vessel." According

to the autopsies, when a drug had a seemingly "idiosyncratic" reaction no such congenital abnormalities were found.

The above described frequency of recurrence and mortality figures are no different than those usually found in the nonpregnant population. The clinical material seems to confirm Walton's (72) and Krieger's (73) opinions that subarachnoid hemorrhage in the pregnant patient is merely a coincidence but, unfortunately, a most grave one.

Among those patients who were treated supportively and allowed to deliver by the vaginal route, there were eight patients who had intracranial aneurysms which had bled,* six patients who had hemorrhage from arteriovenous anomalies (counting multiple births—eleven deliveries), and twenty-one patients the cause of whose hemorrhage was undetermined (multiple birth accounted for seven additional deliveries). Timberlake (75) mentioned five more patients who delivered vaginally, but no details were given. None of these fifty-two pregnancies had any difficulty during labor or the puerperium. Two addi-

TABLE VI
Month of Pregnancy When Subarachnoid Hemorrhage Occurred

	1	2	3	4	5	6	7	8	9	Unknown
Aneurysm	0	2	0	4	6	5	5	4	10	1
Arteriovenous Malformation	0	0	0	2	3	0	1	3	3	0
Unknown Cause	0	3	3	3	3	5	4	9	6	2
Total	0	5	3	9	12	10	10	16	19	3

tional patients had episodes of bleeding prior to pregnancy, during pregnancy and three to five years after normal labor and delivery of a child. One patient, ~~§~~12, had actually had thirty-five episodes of bleeding during her lifetime. The other patient only bled once prior, during and following delivery.

Among 26 patients who were treated supportively and then had cesarean sections, eight had aneurysms; four of them died after the operation—three from recurrent hemorrhage. Three patients had bled from arteriovenous malformations (one patient had two cesarean sections). Fifteen patients bled but the cause was undetermined.

Among those patients who had neurosurgical procedures, twelve patients who had bled from aneurysms were allowed to deliver vaginally, as were four patients whose hemorrhage was due to arteriovenous malformations. One patient whose hemorrhage was undetermined delivered vaginally twice, another had a cesarean section. Three additional patients whose aneurysms were treated surgically had cesarean sections. There seemed to be a tendency

* Since this report was written, one of the author's colleagues has had two patients with documented ruptured aneurysms who subsequently became pregnant. Both women have had normal prenatal courses, uncomplicated delivery by the vaginal route, and normal puerperiums (74).

to allow the patients who had neurosurgical procedures to deliver vaginally on the basis that the surgery had cured the patient.

CONCLUSION

1. A patient who suffers intracranial hemorrhage during pregnancy should have complete angiography as soon as the neurological status allows the procedure to be done (preferably after the first trimester of pregnancy).

2. A woman with a history of subarachnoid hemorrhage may reasonably expect to have a normal pregnancy with the expectation of no recurrent hemorrhage.

3. Clinical experience demonstrates that a woman who has bled in pregnancy may be permitted to deliver vaginally, irrespective of whether intracranial hemorrhage is due to an aneurysm, a vascular anomaly, or is of unknown cause.

4. Cesarean section does not seem to protect a patient from repeat intracranial hemorrhage. Considering the additional morbidity of major abdominal surgery, it seems preferable to deliver these patients from below.

5. There is no definite clinical evidence that labor per se increases the likelihood of subarachnoid hemorrhage from any cause.

6. Although there may be individual idiosyncratic responses to oxytocic drugs, there is no evidence that these medications increase the likelihood of subarachnoid hemorrhage from vascular malformations.

7. Subarachnoid hemorrhage in pregnant patients seems to be coincidental. The clinical course of such a patient does not differ from a nonpregnant patient.

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Subdural Empyema of Odontogenic Origin

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A subdural empyema is a collection of pus between the dura mater and the arachnoid. This layer of pus is of variable thickness and may spread over a part or whole of one or both cerebral hemispheres. The arachnoid membrane is a rather firm barrier between the subdural and subarachnoid spaces. At times this barrier is ineffective and a leptomeningitis may occur. Spread of the infection may also result in associated brain abscesses, thrombosis of the superior sagittal sinus and superficial cerebral veins, and infarctions of the cortex.

In most cases the primary source of infection arises from the paranasal sinuses (usually the frontal sinus) (1 to 3). However, subdural empyema may also be a complication of otitis media and mastoiditis (4), head trauma (5 to 7), infected burr holes (8), or pulmonary infection (9, 10). In rare instances dental infection may be the primary focus.

Cavernous sinus thrombosis (11, 12) and intracerebral abscesses are relatively well known complications of odontogenic infection and of extraction of teeth (13 to 15). Subdural empyema is quite rare. Haymaker (12) reported three autopsied cases, two of which were associated with brain abscesses. Bacchi (16) reported two fatal cases. Peyser's case (17), (our Case 1), will be described in more detail in the present communication.

CASE REPORTS

Case 1. This 31 year old female was admitted to Mount Sinai Hospital in 1954. Three weeks prior to admission to the hospital she had a right lower molar tooth extracted. The reason for the extraction is not known. Two days later she developed right submandibular swelling, which gradually became worse over the next few weeks. On admission, she complained of headaches and a painful swelling of the right side of the jaw. Her temperature was 104°. There was a firm nonfluctuant swelling of the right side of the face and neck and intraorally in the region of the right lower molars. Under local anesthesia, an incision and drainage was carried out in the right inframandibular region and 60 cc of creamy foul pus were evacuated. The culture grew out micrococcus fetidus. Following this therapy, the swelling gradually subsided. However, the patient became apathetic. A few days later she began to have focal left-sided seizures. At this time, she remained drowsy. There was no nuchal rigidity. The cranial nerves were neurologically intact. A left hemiparesis and left extensor plantar response were present. Sensation appeared to be normal. The peripheral white cell counts varied between 10,000 and 19,000 WBC/mm³ with a shift to the left. Skull x-rays were normal. Lumbar puncture revealed clear

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colorless fluid with a normal pressure. There were 20 WBC's/mm³. Total protein was 64 mg%. The spinal fluid sugar was normal. Smear and cultures of the spinal fluid were negative. Over the next few days the patient's condition steadily deteriorated despite antibiotic therapy. She became stuporous, developed bilateral papilledema, a dilated fixed right pupil, and exhibited a left hemiplegia.

Four days later, a burr hole was made in the right parietal region. The dura was opened and thick yellow creamy pus was obtained. An additional burr hole was placed more anteriorly, and the subdural space was irrigated with antibiotic solution. Cultures of the pus grew out micrococcus fetidus. On August 5, 1954, because of an unsatisfactory response to the above treatment, a large frontoparietal bone flap was turned. The dura was tense and, when opened, revealed a thick pyogenic membrane, which contained a large amount of liquid and semisolid pus. The pyogenic membrane was partially removed and the underlying cortex was seen to be swollen and inflamed. There were several small cortical abscesses. The bone flap was discarded and three drains were placed in the subdural space for antibiotic irrigation.

Postoperatively the patient made a good recovery. A cranioplasty was performed on September 10, 1956. When last seen in 1961, she was well except for a mild left homonomous inferior quadrantanopsia and slight left hemiparesis.

Case 2. This 25 year old male was admitted to City Hospital at Elmhurst in 1960, because of headaches, drowsiness, and confusion. Over the preceding few months he had 14 upper teeth extracted because of caries, malocclusion, and "abscesses between his teeth." The last tooth had been extracted about a month before he entered the hospital. The week before admission he began to have generalized malaise, headaches and drowsiness. On admission the patient was drowsy and confused. The temperature was 102°. There was a mild dysphasia and slight right hemiparesis. Cranial nerves were normal. A right extensor plantar response was elicited. Sensation was intact. His neck was stiff and Kernig's and Brudzinski's signs were positive. The white cell count was 27,600/mm³ with a shift to the left. Lumbar puncture revealed turbid fluid under normal pressure. There were clumps of white cells, 90 per cent of which were polymorphonucleocytes. Skull x-rays were normal. A left carotid arteriogram was normal.

The following day the patient developed focal right-sided seizures. His level of consciousness deteriorated and the right hemiparesis became more pronounced despite high doses of antibiotics and anticonvulsant medication. On the fourth hospital day a burr hole was placed in the left temporal region. Yellow pus was encountered in the subdural space. The layer of pus was about 4 mm in thickness. There was no definite pyogenic membrane. The burr hole was enlarged to an adequate craniectomy and the subdural space was irrigated with saline and bacitracin solution. Penrose drains were left in the subdural space for postoperative instillation of antibiotics. Smear and cultures of the pus were negative. The patient made a good neurological recovery. A cranio-

plasty was performed six months later. A recent neurological examination was negative, but the patient still has an occasional grand-mal seizure.

DISCUSSION

Haymaker (12) analyzed 28 fatal cases in which infection gaining entrance into the central nervous system was initiated or precipitated by tooth extraction. The reason for the extraction, oral hygiene, and the number of teeth extracted did not appear to be factors. However, fatal complications of dental infections of the lower jaw were twice as frequent as those of the upper jaw, and were most commonly associated with extractions of molar teeth.

The infection may spread directly through the base of the skull or via the bloodstream. Regional suppurative cellulitis may result in pus burrowing along the fascial planes to the base of the skull, invading the paranasal sinuses or orbit, and then penetrating the cranial cavity by way of a suppurative thrombophlebitis or osteomyelitis. The sphenoid sinus is most frequently involved. Maxillary sinusitis may occur when the floor of the sinus is fractured during tooth extraction. Hematogenous spread occurs more commonly from the lower jaw (12). Intracranial involvement may occur from the drainage of the dental veins into the pterygoid plexus, which anastomoses with the cavernous sinus via the foramen lacerum and foramen ovale.

Several days or weeks following a tooth extraction, the patient may develop local swelling or tenderness. Shortly thereafter signs of intracranial involvement appear rather suddenly. Headaches, signs of meningeal irritation, and diminished levels of consciousness are usually present. Focal phenomena, such as seizures or hemiparesis, are commonly associated with this disorder. Generalized seizures may occur. Fever may vary from 100° to 105°. The peripheral white count is often elevated above 12,000/mm³ and there is a high proportion of polymorphonucleocytes. The spinal fluid pressure may be moderately elevated and the fluid is usually clear and colorless with an increase of cells varying from a few dozen to several hundred. In the typical case, the protein is moderately elevated, the sugar is normal, and the smears and cultures of the spinal fluid are negative for bacterial growth.

Cerebral abscess, which is a more common complication of dental extraction, is usually suspected. The diagnosis of meningitis is often considered, but the fact that the spinal fluid contains only slight or moderate increase in white cells, the normal sugar, the absence of organisms on smear and culture, and the subsequent development of focal signs should lead one to consider the possibility of a subdural abscess. Cortical thrombophlebitis may present an almost identical picture and at times may be extremely difficult to differentiate from a subdural empyema. The problem is further complicated by the not infrequent association of subdural empyema with generalized leptomeningitis and brain abscess (9, 18).

Carotid angiography may demonstrate a subdural mass (19), but may be negative if the collection of pus is thin (as in our Case 2). It is important to proceed with burr hole exploration if the diagnosis is seriously considered. Pus

is usually obtained by a burr hole over the dorsolateral convexity of the cerebral hemisphere. At times the empyema may be located in the superior longitudinal fissure between the falx and the medial surface of the hemisphere (1, 9, 20). Failure to recognize this interhemispheric location may contribute to high mortality. Spread of pus under the falx to the other side may occur.

The mortality rate and incidence of serious neurological sequelae has been high (2, 10, 21, 22). Gurdjian and Webster (18) believe that drainage of the abscess through multiple trephine openings and the instillation of antibiotics through rubber catheters is an effective method of treatment. Poor results with three successive cases treated by multiple burr holes prompted Glass (24) to utilize a large osteoplastic flap, which allows the surgeon to remove more pus, break up loculated collections, and place drainage tubes more advantageously under direct vision without injury to the surface of the cortex. Keith (23) and Botterell and Drake (8) recommend eradicating the infected frontal sinus (when this is the primary source of infection) and removing bone along the midline and frontal region in order to obtain adequate drainage.

Gross (25) reported a case of subdural empyema secondary to frontal sinusitis, which was successfully treated by a large craniectomy and penicillin. Pyser's (17) last four cases have also been treated by this method with good results. Burr holes may not be adequate for sufficient drainage and loculated pockets of pus may not be reached with a limited exposure. Case 1 did not respond to trephines, but eventually recovered after an adequate craniotomy followed by discarding the bone flap. A large craniectomy was carried out in Case 2 with good results. Penrose drains may be inserted into the subdural space for the instillation of antibiotics.

SUMMARY

Two cases of subdural empyema of odontogenic origin are presented. The clinical features and management of this condition are discussed.

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Mallory-Weiss Syndrome—Case Report

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Though tears of the stomach induced by forceful vomiting have been recognized as a cause of gastric hemorrhage since 1929, there have been infrequent reports of this condition in the English literature. Dobbins (1) reported 54 cases including three of his own. In view of the (apparent) rarity of the condition, we feel it may serve a purpose to record the following. We are prompted also by the fact that our patient, who seemed to have an uneventful operative course, died suddenly and unexpectedly soon after completion of the operative procedure. Although there are yet only few operative case reports, this is an uncommon result in cases where the diagnosis is made and treatment carried out early. It may, of course, have no connection with the basic condition.

CASE REPORT

C.H., a 38 year old well-built Negro male, was admitted to Greenpoint Hospital June 3, 1963, at 6:15 P.M. He complained of severe epigastric pain and hematemesis over the preceding four hours. In the past few years he had had some vague epigastric pain unrelieved by antacids. There was no history of hematemesis antedating the present episode. An upper gastrointestinal series at another hospital some twelve months previously revealed no abnormality. The patient was a "moderate" smoker and drinker, and he said he had taken "three drinks the night before admission." Some twelve hours prior to admission, he developed sudden epigastric pain and vomiting which settled soon after. The only fact of note in his past history was an appendectomy ten years before.

Physical examination revealed a well-nourished male of stated age. He was cold and clammy, yet his blood pressure ranged between 160/100 and 130/90 mm Hg.; temperature 98.6°; respirations 22 and pulse 100. Lung fields were clear. No cardiac abnormality was noted. There was some deep epigastric tenderness. The liver was enlarged to two fingerbreadths below the right costal margin; the edge was smooth and nontender. Rectal examination revealed guaiac positive stool. A provisional diagnosis of bleeding duodenal ulcer was made. Other laboratory findings included: hemoglobin 15.6 Gm; hematocrit +31; urinalysis—negative; BUN 15 mg%; glucose 125 mg%; WBC 9,800; x-ray chest and abdomen—no abnormality.

The patient was treated with bed rest; nasogastric lavage with iced saline; and intravenous dextrose in water (5%). At 10:00 P.M., 4 hours after admission, because of continued active bleeding, it was decided to explore his abdomen, believing there was a bleeding vessel in a chronic duodenal ulcer. He

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was premedicated with Demerol 75 mg and atropine 0.4 mg. In the operating room at 10:30 P.M. his blood pressure was 80/50; pulse 100 and respirations 24. Blood replacement was started. General anesthesia was induced with sodium surital 10 mg of 0.5% solution and maintained with cyclopropane 10.5% and oxygen, administered via a cuffed endotracheal tube. Relaxation was obtained with succinylcholine chloride.

Operation

A midline incision provided rapid access to the stomach, which was filled with blood. The duodenum appeared healthy. A gastrotomy was created and the stomach emptied of clot and liquid blood which was seen to run down from above. Careful inspection of the fundus revealed a 5 cm laceration in the mucosa in the long axis of the organ, immediately distal to the esophagogastric junction. At about the middle of the laceration, there was a small vessel pumping into the gastric lumen. The laceration was repaired with one double zero chromic catgut suture. The stomach was sponged clear, and the gastrotomy was closed with two layers of running chromic catgut (00) sutures. The abdominal wall was closed with nonabsorbable sutures. The procedure took a little short of two hours. Blood replacement during the procedure was achieved with two units of blood. The patient's systolic blood pressure was maintained at over 100 mm Hg. except for a ten-minute period immediately prior to operation when it dropped to 80/50 mm Hg.

Thirty minutes after the procedure, while the patient was being returned to the ward, he suddenly collapsed, became pulseless with a nonrecordable blood pressure, and despite resuscitative measures, died.

Post mortem examination showed frothy fluid in both bronchi. The esophagus was normal. The stomach was empty but there were a few small superficial mucosal erosions. In the posterior wall of the stomach, 1 cm distal to the cardio-esophageal junction, the longitudinal tear of the mucosa and submucosa 4.5 cm long, with 1 catgut suture in situ, was found (Fig. 1). The small bowel contained a small amount of altered blood. Microscopic examination of the gastric laceration showed linear destruction of the mucosa and part of the submucosa. Blood and fibrin filled the tear. The arteriolar walls were infiltrated with polymorphonuclear leukocytes.

DISCUSSION

In every series of cases of hematemesis, there is a varying proportion classified "of undetermined origin" even after surgical exploration. It is quite likely that the Mallory-Weiss Syndrome is responsible for some of these. The relative frequency of the condition is emphasized by Atkinson, *et al.* (2) who described eleven cases seen in one area of Britain in "a short period."

Although the condition has been recognized since 1929, it was not until Whiting and Barron's (3) case that a successful repair of the laceration was carried out. Since then, several other successes have been reported.

The exact etiology is still unclear, although it seems likely that forceful straining especially from (excessive) vomiting is the most prominent factor. This straining effect is enhanced in those patients with hiatus hernia, where the lower intrathoracic pressure provides a higher pressure gradient across the gut wall (2). Interestingly, our patient had little in the way of vomiting. Of the eleven patients described by Atkinson, in only four did vomiting precede hematemesis.

Radiological examination is not helpful and the diagnosis must be considered in any patient who is explored for hematemesis in whom no other cause



FIG. 1. Photograph of fixed autopsy specimen showing esophagogastric junction to the right. The linear tear is indicated by the two paper arrows. The suture is close to the left arrow.

can be found. It becomes necessary in such circumstances to perform careful gastrotomy and exclude the tear by careful inspection of the lower esophagus and upper stomach. The existence of the lesion is yet further evidence against performing "blind" gastrectomy for bleeding of undetermined origin.

SUMMARY

An early case of the Mallory-Weiss syndrome is reported. The patient had an unexpected and unexplained demise soon after successful repair of the tear.

Attention is drawn to the necessity of inspecting the esophagus and gastric cardia via a gastrotomy opening in all patients with unexplained gastric hemorrhage who require surgical exploration.

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Chemical Control of Bioelectric Currents in Membranes of Conducting Cells*

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ISRAEL SPANIER WECHSLER

(1886–1962)

It is a great honor to give the first Israel S. Wechsler Memorial Lecture. Israel Wechsler was a dynamic and colorful personality. It is characteristic for his great stature and for the wide scope of his interests that he reached eminence in several entirely different fields.

He was a brilliant neurologist of international reputation. He was Professor of Clinical Neurology at Columbia University, created a strong neurological center at the Montefiore Hospital, and was the Chairman of the Department of Neurology here at the Mount Sinai Hospital from 1938 until his retirement in 1951. He had the great satisfaction that one of his pupils, Dr. Morris B. Bender, succeeded him at the Hospital. He was an outstanding educator and inspiring teacher. His *Textbook of Neurology* is widely used, not only in the United States, but in many countries abroad, and has been translated into several languages. It is now in its ninth edition, the last one having appeared two weeks after his death. In addition he has published more than one hundred original papers on problems of neurology and psychiatry and a scholarly book on *Neuroses*. After the publication of this book, Sigmund Freud invited him to come to Vienna and after two visits there the two men remained in correspondence until the time of Freud's death. Although he accepted many psychoanalytic concepts, he vigorously criticized the unscientific attitude of many analysts.

Israel Wechsler was keenly aware of the rapid advances of neurophysiology and neurochemistry during the last decades. He fully realized the profound impact which basic sciences must have on the future of neurology. Whenever he discussed this future, he considered the field to be in its infancy and predicted vast changes and the development of a much deeper and better understanding of nerve and brain function, based on the spectacular advances of biophysics and biochemistry. It is a testimony to his vision and to his enthusiastic devotion to the field that he had the humility—being an expert and leader in the field—to emphasize time and again the narrowness and the limitation of the present-day knowledge, and that his mind was open to the great revolution taking place in life sciences.

The recognition of his leadership was shown by his election to the Chairmanship of the Section of Neurology and Psychiatry of the Academy of Medi-

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cine, to the Presidency of the New York Neurological Society, and to the Presidency of the American Neurological Association. In spite of his great professional achievements, the intensity of his activities and his interest in many other fields were most remarkable. He was a scholar of unusually high standard not only in English, but also in French and German literature and in European history, being fluent in the three languages. He was an enthusiastic reader of Shakespeare, whose books he always took with him on his many travels.

Coming from Rumania with his parents at the age of fourteen, he was also fluent in Yiddish and Hebrew. He became an ardent and proud American thoroughly dedicated to American idealism and imbued with American concepts. But he also remained deeply attached to the Jewish heritage, to the great ethical and spiritual values of the Jewish prophets, scholars and poets. He had a great knowledge and admiration of Judaism and was an expert on Jewish history. He had many friends among the outstanding scholars of the Jewish Theological Seminary, among them the late Professor Louis Ginzberg, Professors Shalom Spiegel and Louis Finkelstein, and Professor Salo Baron of Columbia University. In recognition of his remarkable work on Maimonides, the Seminary presented him, in 1947, with the Maimonides citation for Jewish scholarship, an extraordinary accomplishment for a man with so many responsibilities and so many activities in his profession.

In addition to this wide range of scholarly activities and achievements, Israel Wechsler's passionate dream and vision was the building up of the Hebrew University of Jerusalem. Having spent his early youth in a small Jewish community in Eastern Europe, he was keenly aware of the frustrating conditions prevailing among the Jews of Central and Eastern Europe, the severe handicaps for the intellectuals, the ominous threats to their existence, although nobody could have foreseen the catastrophe which led to the virtual destruction of most of European Jewry. It was, therefore, not surprising that his idealistic and humanitarian personality led him to Zionism. However, especially at that time, in the 1920's, it was not so much the idea to save Jewish lives and to provide for the existence of as many Jews as possible. He saw alternative solutions for this problem. But it was his ardent desire to provide a place for Jewish scientists, physicians, scholars and poets in a free and creative atmosphere and to build up for this purpose the Hebrew University. This institution would have the special function of being the great center where the Jewish heritage would be cultivated in the ancient homeland and form the basis for the creation of new values for the benefit of the whole of mankind.

His boundless energy and his devotion to the Hebrew University became invaluable for the development of that institution. The general respect for Wechsler's personality as a scholar and as a neurologist made it possible for him to engage the active support of many important people. He was President of the Friends of Hebrew University for many years, and later their Honorary President. He was on the Board of Governors of Hebrew University and, for a few years, Deputy Chairman. His activities brought him into close contact with

many outstanding Jewish leaders who shared his interest, such as Albert Einstein, Chaim Weizmann, Judah L. Magnes, Shemarjah Levin, Chaim N. Bialik and many others. In gratitude for his service and in recognition of his scholarly achievements the Hebrew University conferred upon him, in 1955, the honorary degree of Doctor of Philosophy. In 1959 he was honored by the establishment of the Israel Wechsler Chair in Neurology.

The lively and inspiring personality of Wechsler, the originality of his ideas and concepts, his knowledge in so many fields, his wit and humor, a seemingly inexhaustible wealth of stories, attracted many leading people of our epoch in addition to those already mentioned. He had a large circle of friends among scientists, artists, writers, philosophers, and historians.

Wechsler was an affectionate family man, greatly devoted to his wife, Minnie, and to his daughter, Mrs. Miriam Linn and her family. It was a tragedy that he lost his only son Robert, a young medical student of great promise.

Wechsler's passing was a personal loss to many of us and has left many gaps, but his creative achievements have erected a monument which will continue to live.

* * *

A. THE IONIC PERMEABILITY CHANGES OF CONDUCTING MEMBRANES

More than a century ago it has been established that nerve impulses are propagated along nerve and muscle fibers by electric currents. These currents, in a fluid system such as the living cell, must be carried by ions, as was fully recognized in the nineteenth century. It was also known that the concentration of K ions is high in the cell interior compared to that in the surrounding fluid, while the reverse is true for Na ions. On the basis of simple experiments Overton (1), in 1902, concluded that during electrical activity Na ions enter into the cell interior and an equivalent amount of K ions moves to the outside. The availability of radioactive ions after World War II made it possible to measure quantitatively these ion movements. Studies with squid giant axons by Rothenberg (2) and by Keynes and Lewis (3) fully confirmed Overton's idea. It was found that about $4 \mu\mu$ moles of Na ions enter the axon per cm^2 per impulse and an equivalent amount of K ions moves to the outside. The increased movements of Na ions take place during the rising phase of the action potential, while K ions flow to the outside during the falling phase [Hodgkin (4)].

Theories about the mechanism by which these ion movements are controlled and electric currents are generated and propagated started to develop in the latter part of the nineteenth century when it became known that strong potential differences may develop at semipermeable membranes. Physical chemists, such as Traube, Ostwald, Nernst and others, suggested that nerve and muscle fibers may be surrounded by semipermeable membranes and that permeability changes of these membranes are responsible for electrical activity. The formulation of these ideas best known to biologists is that of Bernstein (5). He proposed that the fibers are surrounded by semipermeable membranes

which, in the resting condition, are permeable for K ions only; they have a positive charge on the outside and a negative one on the inside. When excited, the membrane, due to increased permeability, becomes depolarized and small currents develop between the excited (active) part of the membrane and the resting (inactive) one. These small currents stimulate the adjacent part of the membrane and the same process is there repeated. In this way successive parts of the membrane are excited and the impulse is propagated. Modern concepts are basically similar with the exception that there is not a simple depolariza-

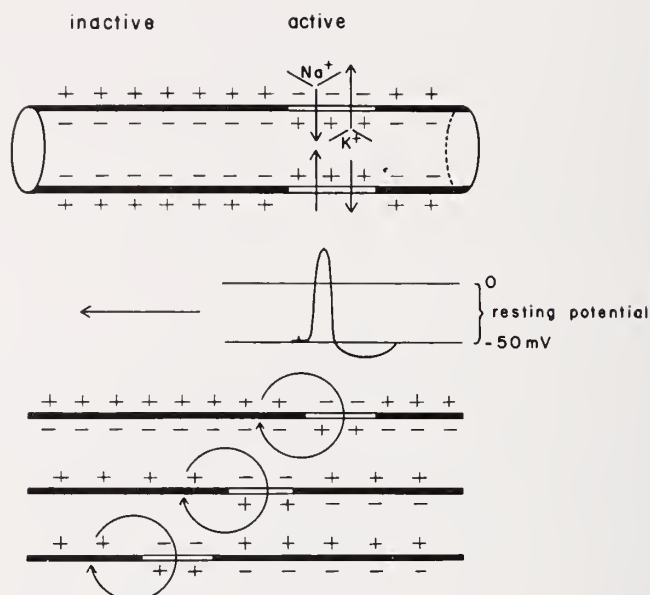


FIG. 1. Schematic presentation of the permeability changes in the conducting membrane during electrical activity. The uppermost drawing shows the reversal of charge in the active point compared to that in the inactive section. Na ions enter during the rising phase of the action potential (drawing below); there is not only a breakdown of the resting potential, but an "overshoot." During the falling phase of the action potential (repolarization) K ions move to the outside. In the lower part the drawings show the activation of three successive points of the membrane.

tion at the excited points, but a reverse of charge, the so-called "overshoot" (Fig. 1), (6, 7).

Until recently, however, the conducting membranes as well as other cell membranes were a theoretical notion, a postulate rather than a well-defined scientific reality. Electron microscopy combined with biochemistry has changed the situation, as in the case of many other subcellular structures. Information has been obtained about structural features and the composition of cellular membranes, about forces controlling the selective transport of substances from the inside of the cell to the outside and vice versa. Robertson (8) has proposed, on the basis of extensive studies, the concept of the "unit membrane" of the structure of cellular membranes, to which belongs the plasma membrane surrounding the cell. The unit membrane has a thickness of about

80 Å and is formed by three layers, a bimolecular leaflet of phospholipids surrounded on the inside and outside by protein layers. The structural uniformity of the different membranes would, of course, not indicate an identity of their chemical forces. Evidence is, in fact, accumulating that in spite of the structural similarities there are considerable variations of chemical composition even in similar types of cellular membranes. Recently, Sjöstrand (9) has reported data on structural features of cellular membranes at variance with those on which the unit membrane concept is based. According to Sjöstrand cellular membranes can be grouped into three different classes with respect to their dimensions; there are also differences of structural patterns. The total thickness of that class of membranes to which belong the plasma membranes he finds to be 90–100 Å; moreover, the plasma membranes are geometrically asymmetric. Sjöstrand interprets his findings to reflect profound differences with respect to molecular structure of the various membranes.

Independent of the problems of structural features, it is certain that the different cellular membranes must have special chemical systems for their many special and diversified functions. The unique feature of the conducting membrane, widely assumed to be identical with the plasma membrane, is its ability to use the ionic concentration gradients, common to other cells, for the generation and propagation of electric currents by changing its permeability in an extremely rapid, precise and reversible way.

It is inconceivable that electricity in a fluid system such as the living cell can be generated and propagated without chemical reactions. Any doubt as to the chemical nature of the processes changing the permeability and controlling the ion movements was removed by the recent heat production measurements of A. V. Hill and his associates (10). Some thirty years ago, Hill and his associates had found that the initial heat produced during activity amounts to only about 2μ calories/g nerve/impulse. This apparent smallness of the initial heat produced was interpreted by Hodgkin (11) as being the result of ion mixing, excluding by implication any chemical reaction taking place in the primary events generating the electric currents. A few years ago, Hill and his associates took up these measurements with much faster recording instruments. Using Maja nerves at 0°C , they found that about 14μ calories are produced/g nerve/impulse, roughly coinciding with electrical activity. This positive phase is followed by a prolonged negative heat taking place within 100–300 milliseconds. The negative heat amounts to about -12μ calories/g/impulse. The initial heat measured previously was the balance of the two phases. However, as the authors point out, the events take place in a membrane which, as mentioned before, is only about 80 Å thick. The heat should therefore be referred to g active membrane material and not to g nerve. In that case the heat produced during electrical activity amounts to about 2 millicalories/g active material/impulse, an amount of heat comparable to that observed in muscular contraction. Discounting other explanations, Hill (12) sees "no alternative to the hypothesis that the early production and absorption of heat after a stimulus are largely due to chemical reactions associated

with, and following, the permeability cycle." Clearly, knowledge of the chemical and molecular forces controlling the permeability cycle is essential for the understanding of the nature of bioelectricity, of the mechanism of nerve impulse propagation.

While the permeability cycle during electrical activity is a unique feature of the conducting membrane, there will be many other functions and chemical reactions not specific for the membrane of the conducting cells. One of them is, for instance, the maintenance, or restoration, of the ionic concentration gradients. The extrusion of Na ions from the interior across the membrane to the outside and the uptake of K ions from the outer environment are processes taking place in most other cells. These uphill movements are slow and require considerable amounts of energy. Evidence is accumulating for the essential role of the energy released by ATP hydrolysis in these processes. Although this problem has been frequently discussed in connection with nerve impulse conduction, it must be recognized that these reactions are a feature common to most cells just as oxidation or glycolysis.

The question which I will discuss in this lecture is that of the specific chemical reactions associated with the permeability cycle during electrical activity, the knowledge presently available, some of the unsolved problems and the perspectives and hopes for the future. This may appear as an ambitious aim; obviously, I can present only a condensed outline and will have to refer frequently to the material which has been published.

B. ROLE OF ACh IN THE CONTROL OF ION MOVEMENTS ACROSS CONDUCTING MEMBRANES

The well-known hypothesis of neurohumoral transmission associated acetylcholine (ACh) with a special part of nerve activity; it assumed that the ester acts as a "mediator" from nerve to nerve or from nerve to muscle. However, the idea was not acceptable to many leading neurophysiologists, among them Erlanger (13), Fulton (14), Lorente de Nó (15) and many others. In view of many similarities between conduction along axons and transmission across synaptic junctions, they did not admit the assumption of a basic difference between the two processes.

Thirty years have passed since the observations were reported which formed the basis of the neurohumoral transmitter theory. The classical methods of physiology and pharmacology which were used in those experiments, in spite of the refinements applied since then, do not permit to analyze the chemical events in a membrane of 100 Å thickness taking place, as the electrical parameters indicate, in milliseconds or less. However, since that time a real revolution has taken place in life sciences. The development of dynamic biochemistry, the spectacular advances in protein and enzyme chemistry, the progress in instrumentation and methodology, such as x-ray crystallography, electron microscopy, optical rotatory dispersion, etc., have provided powerful tools which thirty years ago hardly anybody would have imagined. They have opened nearly unlimited possibilities to study cellular function on cellular,

subcellular and molecular levels. It appeared necessary to reopen the question of the role of ACh in nerve activity and to investigate the problem of bioelectrogenesis, *i.e.*, the forces controlling the ion movements across conducting membranes, by applying the wide range of new methods available.

It was of crucial importance for studying the chemical basis of bioelectrogenesis that, in addition to the general developments, a particularly favorable material was available, the electric organs of electric fish, used by the author for the study of the problems since 1937. Some of the electric organs are the most powerful bioelectric generators created by nature and are highly specialized in their function. The cellular unit, the electroplax, has similar electrical parameters as the nerve or muscle cell. It is only the arrangement in series, as in a Voltaic pile, by which the high voltage of the discharge is achieved. In the electric organ of the electric eel, *Electrophorus electricus*, for instance, in which the discharge amounts to 600 volts, 5000 to 6000 cells are arranged in series (Fig. 2). Although poor in proteins (about 3%) and rich in water (93%), the electric organs of the electric eel and of *Torpedo* hydro-

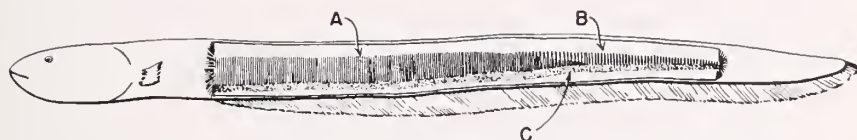


FIG. 2. Diagram of the arrangement in series of the electroplax in the electric organs of the electric eel, *Electrophorus electricus*. The main organ (upper left) forms the largest part, the bundle of Sachs is located near the tail end. Below these two organs is found the organ of Hunter.

lyze 2–4 g of ACh per gram fresh weight per hour. This tissue has been used for the extraction of proteins and enzymes associated with the function of ACh, especially of ACh-esterase, which has been and still is in the center of the chemical and molecular studies. The sequence of energy transformations associated with electrical activity has been established. This information led to the discovery of choline acetylase, the enzyme which forms ACh (16). This was the first enzymatic acetylation achieved in a soluble system, in which it was shown that the free energy released by ATP hydrolysis may be used for acetylation. The hydrolysis and the formation of ACh have been integrated into the metabolic pathways and many chemical and electrical events have been correlated (17–22).

On the basis of these biochemical investigations it became soon apparent that the idea of neurohumoral transmission in its original form had to be abandoned. ACh does not act as a mediator between two cells, its action is an intracellular or an intramembranous process and not limited to the junctions. It has been in many ways established that the ACh system is essential for the control of the ion movements across the membranes of conducting cells during electrical activity. It provides these membranes with the special mechanism which permits the rapid and reversible changes of permeability responsible for bioelectric currents. There is no alternative to this particular

conclusion, no other explanation exists or has even been seriously attempted for the huge amount of data accumulated over a period of more than twenty-five years. ACh is the "specific operative substance" in the elementary processes of conducting membranes in the sense applied by Otto Meyerhof to the role of ATP in the elementary processes of muscular contraction.

Although the essential role of ACh in the permeability changes of the conducting membrane is firmly established, many details still require further investigations. The following theory has emerged as to the role of ACh in the processes controlling the permeability changes (Fig. 3). ACh, in resting condi-

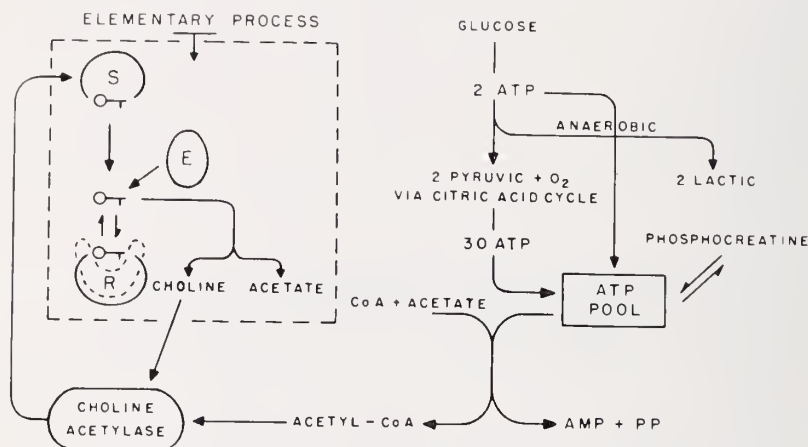


FIG. 3. Schematic presentation of the elementary process controlling the membrane permeability during electrical activity. Integration of ACh into the metabolic pathways. The role of ACh in the permeability cycle may be pictured as follows: 1) In resting condition ACh (ACh^+) is bound to a storage protein (S). The membrane is polarized. 2) ACh is released by current flow; the free ester combines with the receptor protein (R). A conformational change of the receptor (symbolized by dotted line) leads to a shift of charge; this process increases permeability; it is the trigger action by which the ionic concentration gradient becomes effective. 3) The ester-receptor complex is in dynamic equilibrium with free ester and receptor. The free ester is attacked by ACh-esterase (E). 4) The hydrolysis of the ester permits the receptor to return to its original condition. The permeability barrier is re-established and the membrane is repolarized.

tion, is present in a bound form. Any stimulus reaching the membrane (such as, *e.g.*, electric current) leads to a release of the ester which combines with a receptor. Although the receptor has not been isolated as yet, the assumption that it is a protein appears to be the most reasonable one. Proteins have the most flexible and versatile properties such as one would expect from a molecule having the postulated function. Two proteins have been isolated which are associated with its function: the enzyme which produces it and the one which hydrolyzes it. It seems more probable that a third protein rather than an entirely different type of macromolecule has the proper qualities for the receptor and similar although modified active sites as the two enzymes, a view supported by experimental data. In the theory the receptor is therefore assumed to be a protein. In the reaction of ACh with the receptor some change

is produced, probably a change of conformation leading to a shift of charge. The basic principle was first suggested by Kurt H. Meyer in 1937 (23), although at that time only in general terms. It is the reaction of ACh with the receptor which is responsible for the increased permeability and initiates the processes permitting the rapid movements of Na and K ions. The ester-receptor complex is in a dynamic equilibrium with free ester and receptor protein; the free ester is attacked by ACh-esterase and rapidly inactivated by hydrolysis. The receptor (and the permeability) now return to the original resting condition. The barrier is re-established. The permeability cycle initiates a series of other chemical reactions taking place, some of them simultaneously, others successively or in parallel. During the recovery ACh is reformed, Na ions are extruded and K ions taken up, etc.

The ACh system must be assumed to be located in or adjacent to the conducting membrane. Supporting this assumption were some biochemical data (24-26). These were, however, of a more indirect nature. Recently, direct evidence for the localization of ACh-esterase in the membranes has been obtained by electron microscopy combined with staining techniques (27) and by isolation of the membranes with the use of discontinuous density gradients (28). It appears most likely that the system is highly organized in a way similar to that of other multi-enzyme systems in subcellular structures. A structural organization may readily account for the efficiency, high speed and precision of the chemical reactions controlling the membrane changes underlying bioelectric currents.

C. EVIDENCE FOR THE ESSENTIAL ROLE OF ACH IN THE PERMEABILITY CHANGES OF THE MEMBRANES DURING ELECTRICAL ACTIVITY

1. *Significant features of the system.* The huge amount of evidence accumulated in favor of the proposed theory has been summarized in a monograph (17) and in more recent review articles quoted before (18-22). Some of the main features of the evidence may be briefly summarized. Certain requirements had to be met before the theory could be proposed. Obviously, the system must be present in all cells capable of generating and propagating electric currents. The special (although not specific) type of esterase, ACh-esterase, which hydrolyzes ACh, has been demonstrated to be present in various types of conducting fibers throughout the animal kingdom, in motor and sensory, in so-called cholinergic and adrenergic fibers, in central and peripheral, in vertebrates and invertebrates. The concentrations of ACh-esterase are adequate to hydrolyze in milliseconds, *i.e.*, within the first recovery period, significant amounts of ACh. Most nerve fibers may hydrolyze 50-500 μ moles of ACh/g nerve/hr, although some fibers have lower and some higher concentrations. However, the activity should be referred to unit surface area rather than to gram nerve since it is known that the enzyme is essentially concentrated in the region where the conducting membrane is located. Thus, the activity per unit surface area is very much greater than the figures per gram permit to estimate. In recent still unpublished measurements, carried out in

our laboratory by Dr. Miro Brzin with the magnetic diver technique (29, 30), some data of ACh hydrolysis per unit surface have been obtained. In the squid giant axon the figures are 10^{-15} mole of ACh hydrolyzed per cm^2/msec . Assuming 3 to 4-fold excess and 2–3 msec required for the removal of ACh released per impulse, 1 molecule of ACh would be metabolized per 1000 to 2000 Na ions entering the interior in these axons. This is, of course, only a rough approximation. In other fibers the activity per cm^2 per unit membrane surface area was found to be 30–50 times higher. It may be recalled in this connection that the extraordinary activity of ACh-esterase in electric tissue, highly specialized for bioelectrogenesis, can hardly be considered as an accident of nature.

Choline acetylase, the enzyme which forms ACh, is also present in all conducting fibers tested, although in markedly lower concentrations (19). This is not surprising since the formation of ACh is a slow recovery process and not directly associated with electrical activity, as is the case with ACh-esterase. The objection raised that the concentration of this enzyme in some sensory fibers (dorsal roots) is too low to be compatible with the theory has no validity, as has been recently discussed in detail (19). In unmyelinated sensory fibers choline acetylase was recently shown to be quite high (31).

Among the prerequisites required for assuming a special chemical reaction to be associated with the permeability changes in the conducting membrane that of an extraordinarily high speed is of particular importance. The whole permeability cycle takes place within about 1–3 msec, according to the type of fiber. The peak of the spike of the increase in permeability is reached within 100 μsec . Obviously, only a chemical reaction with a comparable speed may be postulated to be associated with this electrical activity. ACh-esterase is one of the fastest-acting enzymes known. According to the latest evaluation of Lawler (32) the turnover time of the enzyme is at most 30–50 μsec , probably smaller, a speed fully adequate for the postulated function.

2. *Inseparable association of electrical and ACh-esterase activity.* The prerequisites mentioned, although pertinent and suggestive because of their extraordinary character, cannot be used as evidence for the proposed function. A crucial test requires the demonstration of a direct correlation between electrical activity and the reaction of ACh with the two proteins postulated to be involved in the permeability cycle, the receptor and ACh-esterase. If the proposed concept is correct it should be impossible to separate electrical activity from the functioning of these two proteins. Block of either the one or the other by competitive and potent specific inhibitors should block conduction. Although the two proteins are located in close vicinity and each inhibitory compound related in structure to ACh may react with the active site of both proteins, the affinities to each of them vary greatly, in some cases by several orders of magnitude. This makes it possible to decide which of the two proteins is affected by the action of a compound.

Competitive and potent inhibitors of ACh-esterase applied to a great number of different types of nerve fibers, under a variety of conditions and with

different procedures, block electrical activity. Under no conditions has it been possible to separate electrical and ACh-esterase activity. If the enzyme activity falls to a low level, conduction inevitably fails, thus demonstrating the essential function of the enzyme in the permeability cycle. Physostigmine has long been known as a potent competitive and reversible inhibitor of ACh-esterase. The dissociation constant of the enzyme inhibitor complex is 1×10^{-7} . The compound reversibly blocks electrical activity in all types of conducting fibers: motor and sensory, sympathetic and parasympathetic (so-called cholinergic and adrenergic), central and peripheral, vertebrate and invertebrate, and in muscle.

Organophosphorus compounds are another type of potent inhibitors, but this inhibition is "irreversible" in the sense that the enzyme can only be reactivated by chemical action, but not by dilution or dialysis, as in the case of competitive reversible inhibitors. These compounds are for several reasons useful tools for studying the relationship of electrical and enzyme activity; there are, however, many pitfalls in such analysis (17, 18). At first it was thought that it is possible to inactivate the enzyme completely, while electrical activity was still unimpaired (33). Critical evaluation of these and subsequent data has revealed that invariably some of the many pitfalls had been overlooked and inadequate procedures had been used. There is an excess of enzyme, but as soon as the enzyme activity falls below a certain minimum level, electrical activity is blocked. But even after complete irreversible block of conduction some enzyme activity still remains. In no instance has it ever been possible to separate electrical and enzyme activity.

The question was raised why the concentration of an inhibitor required to block conduction is so much higher than that required to inhibit the enzyme in solution. Such a question overlooks completely the fundamental difference between the action of enzyme inhibitors used in solution and that applied to intact cells or tissues. Much of the enzyme present in cells (or tissues) is either poorly or not at all accessible to compounds applied externally, since some of them do not penetrate into the cell and others only in a very small fraction of the outside concentration. Neostigmine, for instance, a lipid insoluble compound, does not enter all (34). This will be later discussed in more detail. But even when a highly lipid soluble compound is applied, such as diisopropylphosphofluoridate (DFP), the inside concentration is only one-thousandth of that on the outside at the time at which electrical activity is blocked (35). The importance of structural barriers for the apparent (not real) potency of an inhibitor has been strikingly demonstrated by Dettbarn (36) with the frog sciatic nerve. In this nerve there are present several 1000 heavily myelinated fibers, surrounded by a fat, connective tissue and a sheath. Applied to the whole nerve, 5 mg of physostigmine per ml are required to block electrical activity in 30 min. When, however, a single fiber is isolated and the inhibitor is applied in a few $\mu\text{g/ml}$ to a single node of Ranvier, electrical activity fails within a few minutes. The apparent potency has increased more than one-thousandfold.

3. *Essentiality of ACh receptor for electrical activity.* Although an ACh receptor has been postulated for a long time, its existence as a cell constituent distinct from ACh-esterase has been experimentally demonstrated only in recent years. Since some compounds related in structure to ACh have a high affinity to the receptor and a low one to the enzyme, it is possible to block electrical activity by compounds acting on the receptor without affecting the enzyme activity. Compounds with high affinity to the enzyme, on the other hand, block only when the enzyme activity has decreased to a low level. This evidence has first been obtained on the eleteroplax (37) and more recently by Dettbarn (38) on lobster axons which are suitable for this type of experiments for reasons to be discussed later.

The compounds acting only on the receptor have been divided into two different types according to the way they affect the electrical parameters (37). One type blocks electrical activity without depolarization, indicating that the barrier to ion movements remains unchanged; in the other case the barrier is reduced in a way comparable to that prevailing during activity. Quaternary compounds such as ACh, carbamylcholine, decamethonium, neostigmine and others usually belong to the latter category, whereas most tertiary analogues such as for instance procaine, tetracaine and the tertiary analogue of neostigmine belong to the former category. If one associates the transient change of permeability in the conducting membrane with the reaction between ACh and receptor, one must assume that ACh not only combines with the receptor but produces a simultaneous change. We have, therefore, introduced, in analogy with substrates and inhibitors in enzyme chemistry, the distinction between receptor activators which effect this change, and receptor inhibitors which combine with the active site of the receptor but are unable to produce the change and apparently prevent ACh from acting; these latter compounds are competitive inhibitors ("antimetabolites").

Of great importance for the study of the interaction of ACh and related structures with the receptor has been the development of a monocellular electropilax preparation by Schoffeniels (39, 40). A single electropilax is dissected from the Sachs organ of *Electrophorus* and kept between two nylon sheets, one with a window adjusted to the dimensions of the cell, the other with a grid consisting of nylon threads by which the cell is pressed against the window (Fig. 4). The two sheets containing the cell between window and grid are mounted between two blocks of lucite, each containing a pool of fluid (Fig. 5). When the two blocks are fixed, the cell separates the two pools of fluid so that ions or other dissolved substances cannot pass from one pool to the other except through the cell. Only one face of the cell is innervated and has the conducting membrane, while the other face, which is richly folded, is not innervated and nonconducting (Fig. 6). The fluid of one chamber bathes one type of membrane, that of the second chamber the other type. The innervated membrane of the electropilax has a rectangular shape: the preparation, therefore, is suitable for the study of ion movements across the membranes. With the use of radioactive material and appropriate arrangements, the preparation per-

mits one to follow the rates of ion flux across the two membranes separately, to study physical and chemical factors affecting it and to measure changes of electrical parameters simultaneously (41, 42, 43, 44). A series of improvements have been introduced during recent years by Higman, Bartels and Podleski (45-47), especially a switching device which permits the measurement of the potential difference across the conducting and the nonconducting membrane with intracellular electrodes and across the whole cell. Due to its extreme sensi-

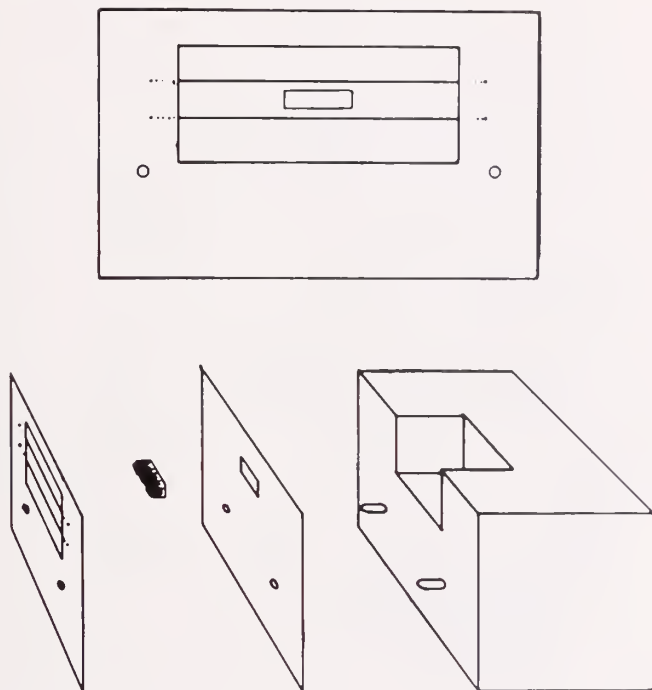
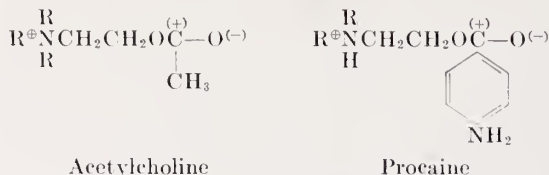


FIG. 4. Diagram presenting the arrangement in which a single isolated electroplax separates two pools of fluid. The drawing shows the respective position of one chamber for the pool of fluid, the sheet of nylon containing a window, the single electroplax, and the grid used for pressing the cell against the window. The second chamber is not shown in the drawing.

tivity to the smallest modification of the chemical structure of compounds reacting with the receptor, the preparation has become a unique and useful tool for examining the action of ACh and related compounds on the receptor to study structure-activity relationships and to correlate the action to the effect on electrical parameters. The results are readily reversible and remarkably reproducible with cells of different specimens. An experiment with ACh, shown in Figure 7, illustrates the rapid and completely reversible block of electrical activity by ACh and the simultaneous depolarization of the membrane (78). Figure 8 shows the block without depolarization by a receptor inhibitor (tetracaine).

Pertinent for the topic under discussion were the observations on the effects

of the local anesthetics procaine and tetracaine on this preparation. These two compounds are analogous in structure to ACh:



The substitution of a methyl group on the N atom by a proton makes this com-



FIG. 5. Photograph of the chambers, used for the monocellular electropex preparation, shows the position of the window and the threads of nylon between the two pools of fluid. On the right side of the picture one sees the two tubes for the air lift.

pound lipid soluble since at neutral pH part of the molecules are in an uncharged form. Lipid solubility is still further enhanced by the substitution of the methyl group on the carbon of the carbonyl group by an aniline ring. In tetracaine one hydrogen on the N of the aniline is substituted by a butyl group.

These compounds are typical receptor inhibitors with a low affinity to the esterase; they act like typical antimetabolites, abolishing the effect of the externally applied ACh at the junction and that released internally in the conducting membrane. The competitive mode of action has been demonstrated in experiments on the monocellular electropex (45, 47). It is particularly apparent by the contrast to a compound such as the puffer fish poison tetrodotoxin which blocks electrical activity in low concentrations, but has no affinity to

ACh-esterase or receptor. No antagonistic action is observed between this toxin and ACh or related compounds.

The evidence that procaine and tetracaine act as antimetabolites by competition with ACh explains the mode of action of local anesthetics as a chemical

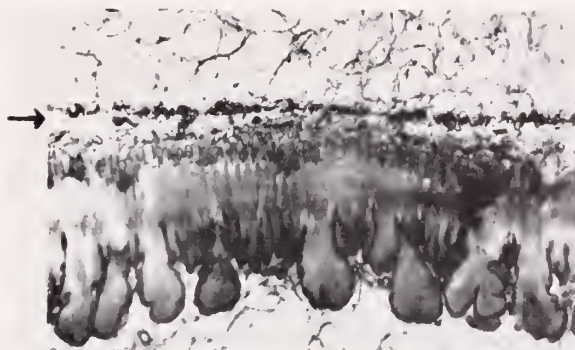


FIG. 6. Microscope picture of a cross section of a single electroplax in the bundle of Sachs of *Electrophorus electricus*. Only the one face of the electroplax (the upper one in the picture) is innervated; the deeply folded other face is not innervated. The arrow indicates the space between the connective tissue surrounding the adjacent compartment and the innervated membrane. In the dissection the connective tissue membrane of the adjacent compartment must be removed.

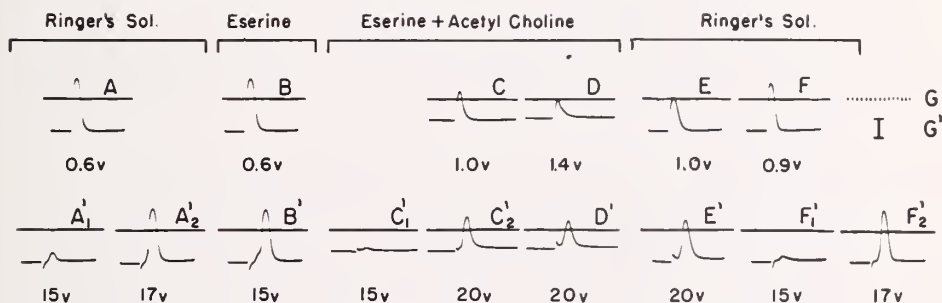


FIG. 7. Effect of ACh on the resting and action potentials of a single isolated electroplax. The Figure shows the inseparable association of the blocking and the depolarizing action. The recordings were made with the cathode ray oscilloscope by means of microelectrodes, one of them intracellular. The value for the resting potential, measured by the distance between the two base lines is usually about 85 mV. A-F direct, A'₁-F'₂ indirect stimulation. The voltages refer to stimulus strength. A-A'₂ control in Ringer's solution; after A-A'₂ physostigmine 5×10^{-5} M added at 0 time; B, B' 5 min. later. ACh 5×10^{-6} M + physostigmine 5×10^{-5} M added at 5½ min.; C-C'₂ 30 sec., D, D' 32 min. later. Returned to Ringer's solution at 9½ min. after 0 time. E, E' 1 min., F-F'₂ 15 min. recovery. Calibration in this and the following Figure: 1000 cycles/sec. and 50 mV (78).

reaction with a specific chemical cell constituent. At the same time the data offer evidence for the postulated role of ACh in the conducting membrane by demonstrating the inseparable association of electrical activity with the receptor since it is well known that these local anesthetics are capable of blocking electrical activity in all conducting membranes.

The receptor protein has not been isolated as yet. A protein isolated by

curare precipitation from electric tissue of *Electrophorus* and thought to be a single component with a high affinity to curare (48) has been resolved by column chromatography into at least 4-5 components. None of the proteins had a high affinity to curare (49). The conclusions of the earlier work have thus been invalidated.

D. MOLECULAR FORCES IN ACh-ESTERASE AND RECEPTOR

The momentous discovery of Engelhardt and Ljubimova (50, 51) that myosin reacts with ATP in a way postulated by theory and acts as ATP-ase opened a new chapter in the efforts to explain how chemical energy is transformed in the living cell into mechanical energy during muscular contraction. The interest of many investigators in many laboratories has since that time centered around the problem of the precise interaction of ATP with the structural proteins of muscle. The last twenty-five years have seen great achievements of these efforts in many laboratories and molecular levels have been reached (see, *e.g.*, 52-55). Of crucial importance for the final understanding

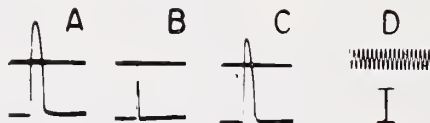


FIG. 8. Effect of tetracaine (a receptor inhibitor) on the resting and action potentials of a single isolated electroplax. The compound blocks electrical activity but with depolarization. Recordings as in the preceding Figure. Only the response to direct, but not to indirect, stimulation is shown, since in both cases the resting potentials remain unchanged. A: Control in Ringer's solution; B: 5½ min. after the addition of tetracaine 5×10^{-5} M. Returned to Ringer's solution at 6 min.; C: 11 min. recovery; D: Calibration (45).

will be the answer to the question of what exactly happens with actin and myosin in their interaction with ATP during the moment of contraction.

A similar situation prevails in the problem of the chemical events effecting the permeability cycle in the conducting membrane during electrical activity. For the ultimate answer it is necessary to analyze the macromolecules in the membrane and their behavior in their interaction with small molecules. The assumption that the permeability of a membrane may change in a specific way without an active participation of macromolecules would be difficult to reconcile with all the information available today concerning the function of living cells. During the last fifteen years a considerable amount of information has accumulated about the interaction of ACh with the proteins associated with its function and has contributed to the understanding of the generation of bioelectrogenesis on a molecular level. It appears likely that some of the main advances in the field in the years to come will result from the further analysis of the macromolecules involved in the permeability cycle of the conducting membrane.

1. *Mechanism of ACh hydrolysis by ACh-esterase.* ACh-esterase is by far the most suitable protein for the analysis of the molecular forces acting between ACh and the proteins associated with its function. It is readily avail-

able in a highly purified state; rapid and convenient methods are available for measuring the activity of the enzyme; it reacts with a wide variety of substrates and inhibitors, *i.e.*, it is not too specific and nevertheless not too unspecific for such studies. Detailed descriptions of these investigations may be found in various review articles (17, 56).

Studies with a great variety of appropriate substrates and inhibitors have revealed that the active site of the enzyme is subdivided in two spatially and functionally separated groups, an anionic site reacting by Coulombic and Van der Waals' forces with the quaternary nitrogen group, and an esteratic site, forming a covalent bond with the carbon of the carbonyl group. It is today well established that in the Michaelis-Menten complex formation this elec-

Fig. 9. Schematic presentation of the interaction of the active groups in the surface of ACh-esterase and the substrate (Michaelis-Menten complex). The O atom in the active site is that of serine; B: symbolizes a second nucleophilic group, presumably an imidazol ring of a histidine.

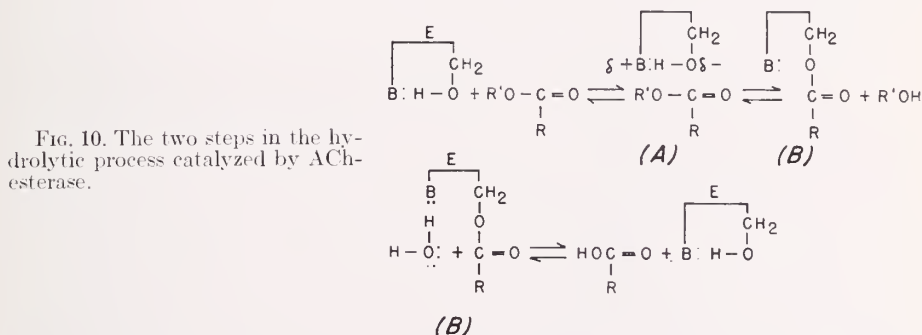
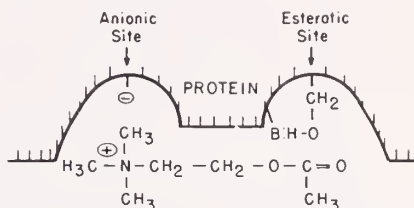


Fig. 10. The two steps in the hydrolytic process catalyzed by ACh-esterase.

trophilic carbon reacts with the nucleophilic O atom of a serine molecule in the active site, present in ACh-esterase as well as in other esterases and ester-splitting enzymes (57, 58). A tentative scheme of the forces acting in the Michaelis-Menten complex formation is given in Figure 9. In addition to the nucleophilic O atom there must be a second nucleophilic group, indicated in the Figure as B, for accepting the proton released in the process. It appears likely that this nucleophilic group is the imidazole ring of a histidine (59). The hydrolytic process takes place in two steps (Fig. 10). In the first, the alcohol (choline) is eliminated by an electronic shift and an acetylated enzyme formed; in the second step the acetylated enzyme reacts with water to form acetate and restored enzyme (60).

2. *Organophosphorus compounds.* The analysis of molecular forces acting between ACh and the enzyme has provided pertinent information concerning the processes taking place in the membranes of conducting cells. One illustra-

tion is the elucidation of the mechanism of action of organophosphorus compounds which, as mentioned before, are potent inhibitors of ACh-esterase. These compounds have long been used as insecticides. Some of them are volatile and were developed during World War II as the well known "nerve gases," potentially the most powerful chemical warfare agents. Although the organophosphates react with a variety of ester-splitting enzymes, the fatal action of these compounds must be attributed to a block of ACh-esterase in view of its vital function; they produce a specific biochemical lesion.

Burgen (61) has suggested that these compounds may block the enzyme by phosphorylation, a reaction in which the acidic group is eliminated and the phosphoryl group is transferred to some polar group on the enzyme. This suggestion has been fully confirmed once the hydrolytic process was understood. The nucleophilic group which, as we have seen before, is the O atom of the serine, attacks the P atom in an S_N2 reaction (62). However, instead of an

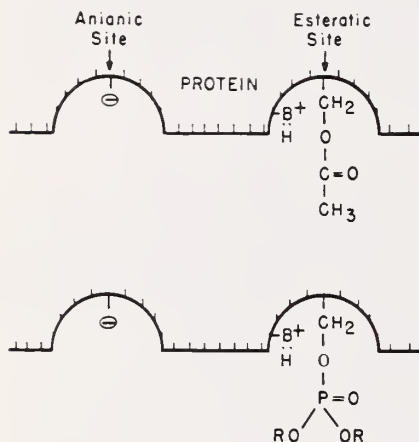


FIG. 11. Schematic presentation of the acetylated enzyme (upper row) compared to the phosphorylated enzyme (lower row).

acetylated enzyme, the physiological intermediary, a phosphorylated enzyme is formed (Fig. 11). Whereas the acetylated form reacts extremely fast, within a fraction of a millisecond, with H_2O to form acetate and restored enzyme, the phosphorylated enzyme does not react with water at all or does so extremely slowly, requiring a period of days or weeks. The enzyme is inactivated and death ensues.

Once the mechanism of organophosphate action was understood, it seemed possible to reverse the inhibition by a displacement reaction in which a nucleophilic group would attack the P atom and break the P-O bond; thereby the enzyme activity would be restored. Hydroxylamine is a nucleophilic agent which had been shown by Hestrin (63) to form acethydroxamic acid, a reaction catalyzed by the enzyme; the compound attacks the carbon of the carbonyl group of the acetylated enzyme. Hydroxylamine was indeed found to reactivate the phosphorylated enzyme (64), although slowly and only in high concentrations. ACh is a greatly superior substrate of ACh esterase compared to ethyl acetate. The presence of the quaternary group increases the force of

binding by more than a thousandfold. It thus seemed possible that a quaternary nitrogen group attached to a nucleophilic group in a proper distance might promote the reactivation. A series of compounds of this type was developed by Wilson and Ginsburg. Among these compounds pyridine-2-aldoxime methiodide (PAM) was found to be the most potent reactivator of the phosphorylated ACh-esterase (65). A number of similar compounds were developed at about the same time by Childs *et al.* (66). PAM reactivates many organophosphates, among them sarine and DFP, although others are only poorly reactivated or not at all (see, *e.g.*, 17, 18).

If the fatal action of organophosphates on animals is due to the postulated specific biochemical lesion, *i.e.*, to the inhibition of ACh-esterase, PAM might be an efficient antidote. This proved to be the case: when PAM was tested by Kewitz on animals, especially in combination with atropine, which protects the receptor protein, the animals survived 10 to 20-fold lethal doses of DFP (67). PAM was tested in Japan on a large scale by Namba and Hiraki (68) on humans suffering from poisoning by exposure to organophosphorus insecticides. In that country these insecticides are of vital importance for protecting the rice crop. The success of the treatment was striking and many lives were saved. Today PAM is used in insecticide poisoning in many countries. It has recently been officially accepted by the Food and Drug Administration. It has been shown that in PAM treated animals ACh-esterase is reactivated, *i.e.*, the biochemical lesion is repaired (69, 70).

The reactivation of ACh-esterase by PAM offers the possibility of a crucial test of the essential function of the enzyme in conduction. As will be discussed later, ACh, PAM and other lipid insoluble quaternary nitrogen derivatives do not penetrate the structures surrounding conducting membranes. Recently, however, Dettbarn and Davis (71) discovered that the conducting membranes of the axons of the lobster walking leg are sensitive to ACh except during a certain season. Therefore, PAM should in this preparation also be able to penetrate the surrounding structure and reactivate phosphorylated ACh-esterase in the membrane. The axons were, therefore, exposed to Para-oxon until electrical activity was irreversibly blocked; then the axons were treated with PAM. Electrical activity returned, whereas in the control axons, washed with saline, the block was irreversible (72). We have seen that organophosphates phosphorylate the O atom in the serine at the active site of ACh-esterase and that this P-O bond is broken by PAM in a highly specific way. Thus, formation of this P-O bond blocks electrical activity, the dephosphorylation, effected by a specific chemical reaction, restores electrical activity.

3. *The effect of ACh on the receptor.* Another series of experiments illustrates how the understanding of molecular forces acting in the reaction between ACh and its functionally associated protein has provided interesting information concerning the events in the permeability cycle of the conducting membrane during electrical activity. The theory assumes that conformational changes of the receptor protein in the reaction with ACh produce a shift of

charge which triggers a sequence of events leading to the specific movements of ions. This theory is in line with the ideas discussed by Kurt H. Meyer (23) and T. Teorell (73).

The idea of conformational changes of proteins during their reaction with micromolecules is today widely admitted. A classical example are the strong structural changes of haemoglobin during its combination with oxygen, well documented by x-ray crystallography and kinetic studies (74). A discussion of the general problem of conformational changes of enzymes in their active state may be found in Koshland's review (57). Indirect evidence for conformational changes of the proteins of the ACh-system has been obtained with three members, the receptor and the two enzymes, ACh-esterase and choline acetylase. If the *binding* of an ammonium ion to ACh-esterase is compared with that of the compounds in which the protons of the ammonium ion are successively replaced by methyl groups, three of the methyl groups, but not the fourth, contribute substantially to the binding. Since tetramethyl ammonium has a tetrahedral structure, *i.e.*, a more or less spheric shape, the fourth methyl group would not be in direct contact with the protein surface, but would stick out in solution; therefore, it would not contribute to the binding by Van der Waals' forces. In contrast, if the hydrolysis of ACh and its tertiary analogue are compared, the extra methyl group greatly promotes the enzyme *activity*. The rate of acetyl enzyme formation is tenfold increased (75). A corresponding effect has been demonstrated with choline acetylase (76). These effects may best be explained by conformational change during the reaction in which the protein surface envelopes the fourth methyl group. A conformational change is further suggested by studies of the entropy of activation (ΔH^\ddagger) of the hydrolytic process catalyzed by ACh-esterase. The entropy of activation is very favorable in the case of esters having a quaternary group in contrast to the unfavorable entropy in the absence of the extra methyl group (77).

The strong promotion of the two enzyme reactions by the extra methyl group has found a striking parallelism in experiments comparing the reaction of ACh and its tertiary analogue with the receptor on the monocellular electroplax preparation (78). Dimethylaminoethyl acetate is 200 times less potent than ACh. Removal of the second methyl group further decreases the potency, but only by a factor of 20. This latter difference may be attributed, at least partly, to the stronger binding by the second methyl group. But the increase in potency by a factor of 200, due to one additional methyl group, would be difficult to explain by Van der Waals' forces. Binding is only part of the interaction between small and large molecules. The assumption of conformational changes of the protein during the interaction with ACh and related micromolecules may possibly be tested with optical rotatory dispersion and related techniques, such as circular dichroism, which may permit one to detect even small conformational changes such as must be assumed in these interactions. Such measurements are being prepared by Dr. S. Beychok for all three proteins reacting with ACh.

In a recent paper Hodgkin and his associates (79), discussing the nature of the permeability changes, distinguish between two views: according to the one, depolarization causes charged particles or carriers to move to new positions; according to the second, chemical reactions are responsible for the permeability changes. This distinction does not present the real difference. Shift of charge has been the basic assumption of Meyer's and Teorell's views some thirty years ago. Meyer attributed the shift of charge to a folding or unfolding of a protein; essentially the same principle has been assumed by the author, only modifying it by attributing the conformational change specifically to the action of ACh on the receptor as being the molecular process responsible for the permeability change. The question of what kind of charged particle is responsible is left open by Hodgkin *et al.* Although not excluding a chemical reaction, they see a restriction for the chemical theory in the fact that in this case the system must be tightly bound to the membrane. Such an assumption does, however, not offer a serious difficulty in view of the experience with other functionally active subcellular structures in which the components are tightly bound, and the many indications of the structural organization of the ACh system and its association with the membrane.

Another statement of Hodgkin and his associates also requires clarification. They assume that in the chemical theory the free energy of ACh hydrolysis plays an essential role. Actually, the hydrolysis of ACh restores the original barrier, *i.e.*, it is the primary recovery process; it ends the permeability cycle but does not initiate it. The primary event, as pointed out before, is the reaction of ACh with the receptor. The enthalpy (ΔH), although not the free energy (ΔF), of ACh hydrolysis may contribute to the initial heat production which roughly coincides with the action potential and thus covers the whole permeability cycle. Although the available data permit only rough and tentative approximations, it seems that the enthalpy of ACh hydrolysis may indeed contribute a few per cent to the initial heat, as has been discussed elsewhere (22). However, ACh hydrolysis almost certainly forms only one part of the reactions which are the source of the initial heat, the enthalpy of the reaction of ACh with the receptor may be another factor; breaking of hydrogen bonds, release of protons, ion dilution, and other secondary reactions coupled with the primary processes may all be contributory factors.

4. *Excitatory and inhibitory effects of ACh.* It has long been known that in some fibers ACh depolarizes and stimulates, while in others (for instance heart) it hyperpolarizes and inhibits the membrane. In fact, in the Aplysia ganglion two types of cells have been demonstrated to exist side by side, reacting to ACh in opposite ways (80). Depolarization results from increased Na, hyperpolarization from increased K ion conductance. This apparently opposite effect finds its parallel in the interaction of ATP and actomyosin: ATP was first found to be necessary for contraction but later also for relaxation. Whether it acts in one or in the opposite way depends on the so-called relaxing factor, first described by Marsh (81) and Bendall (82) and identified today

with calcium movements controlled by the endoplasmic reticulum (83-85). Similarly, whether ACh has a depolarizing or hyperpolarizing action probably depends on secondary controlling factors. The action of ACh must be coupled with additional reactions taking place simultaneously or subsequently as all cellular reactions. There is, for instance, some indirect indication that Ca ions may be closely associated with the ACh system. Ca ions strongly react with anionic polyelectrolytes [Katchalsky (86)]. Release of Ca ions may lead to rearrangements of polyelectrolytes required for the acceleration of Na and K ion movements. While such effects appear possible, they are at present speculations. The available data do not permit an answer to the question whether Ca ions play a crucial role in the permeability changes and still less what the mechanism of this action may be. In any event, the participation of Ca ions does not remove the necessity of a specific and reversible chemical trigger action such as postulated and documented for the ACh system.

E. SIMILARITY OF THE ROLE OF ACH IN AXONAL CONDUCTION AND SYNAPTIC TRANSMISSION

Only a few years ago the view was expressed (17) that the evidence in favor of the action of ACh controlling the permeability changes in conducting membranes during activity was conclusive; but although a similar function of ACh in the pre- and postsynaptic membranes of the junction appeared likely, in this case the postulated role was admittedly based on indirect evidence and on analogy, and therefore less conclusive. The developments of the last three years have drastically changed the situation. Crucial and direct evidence has been obtained which supports the unified concept and contradicts the idea of an *intercellular* role of ACh between two cells at the junction. The new data clearly indicate that the function of the ACh system is essentially similar at the junction to that in the conducting membrane.

The assumption of neurohumoral transmission was essentially based on three sets of observations. 1) ACh and curare have a very powerful action on the junction. In contrast, they fail to affect axonal conduction even when applied in high concentrations. 2) ACh appears in the perfusion fluid following nerve stimulation. 3) When the nerve fibers are sectioned and the endings have degenerated, no ACh is detectable in the perfusion fluid, if the muscle is directly stimulated; thus, the ACh found in the perfusion fluid must have been secreted from the nerve terminal. These three lines of observations were accepted as a conclusive evidence for the hypothesis; all three have found explanations supporting the unified concept.

1. *Action of ACh and curare on the axonal membrane.* Curare and ACh are quaternary nitrogen derivatives and insoluble in lipids. The conducting axonal membranes, in contrast to those at synaptic junctions, are surrounded by structures rich in lipid material which form a permeability barrier preventing lipid insoluble compounds from reaching the membrane and acting on the excitable mechanism. This explanation of the failure of ACh and curare to act on the conducting membrane was supported by experiments on the squid giant

axon. On exposure of the axons to neostigmine or N^{15} labeled ACh it was found that the compounds did not penetrate into the interior of the axon in contrast to lipid soluble tertiary nitrogen derivatives (34, 87). However, recently actions of ACh and curare on the electrical activity of axons have been obtained, as postulated by theory, in two different ways: either special preparations were used where the barriers are weak, or axons were chemically pretreated in order to reduce the barrier.

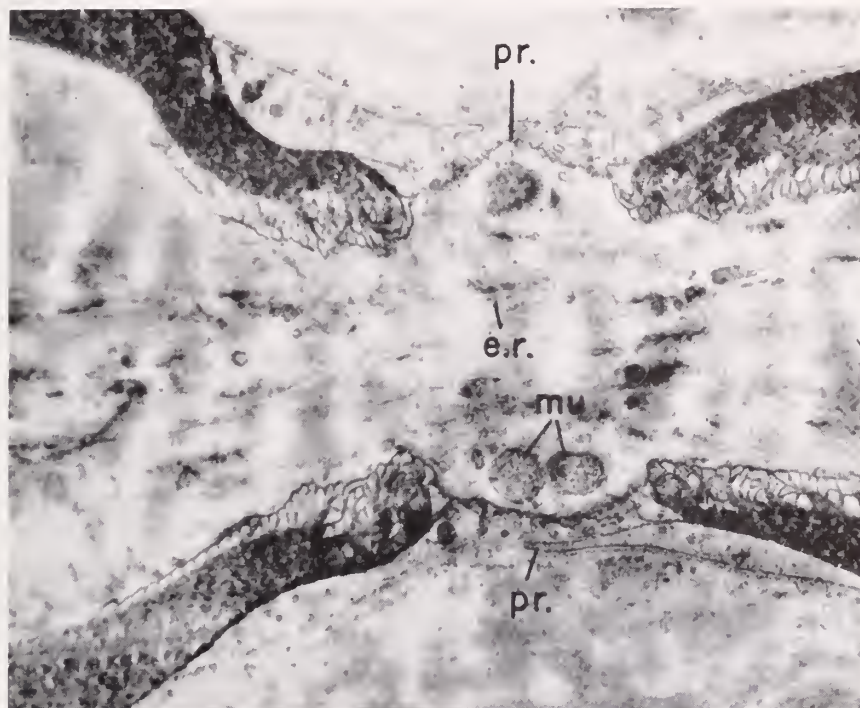


FIG. 12. Longitudinal section of a Ranvier node fixed in permanganate. The unmyelinated nodal region is characterized by a collar of minute processes (pr) of the two Schwann cells meeting at the node. Magnification: $\times 16000$ [from Robertson (8)].

In his famous experiments Claude Bernard applied curare to the frog sciatic nerve formed, as mentioned before, by several thousand myelinated axons surrounded by a large amount of connective tissue, fat and a sheath. Obviously, the compound will not be able to penetrate all these barriers, in contrast to the situation at the junction, where the membranes are poorly (or not at all) protected. However, electron microscopy has revealed that at the Ranvier node the axons are poorly protected, although even there is still a thin structure covering the conducting membrane (Fig. 12), (8). Dissecting one single fiber from the frog sciatic nerve and applying curare to a single Ranvier node, Dettbarn (88) obtained rapid and reversible block of electrical activity of this axon in a similar way as is known for the neuromuscular junction. Thus,

the claim has been substantiated that the failure of curare to block axonal conduction is due to structural barriers protecting the conducting membrane in the axon. The removal of these barriers exposes the excitable mechanism of the membrane to the action of curare.

A direct effect of ACh on the electrical activity of the axonal membrane has been demonstrated by Dettbarn and Davis (71, 89). The axons in the fibers of the walking leg of lobsters are apparently relatively poorly protected, as suggested by electron microscope examination. When applied to the whole bundle of fibers, formed probably by more than 1000 axons, ACh depolarizes the fiber and blocks electrical activity. The effect is readily reversible. Decamethonium and succinylcholine also block reversibly axonal conduction of these axons (90); curare was also effective when the high Ca ion concentration of sea water was reduced and Mg ions were omitted. The strength of these effects seem to be subject to seasonal variations.

A direct effect of ACh was also observed by Arnett and Ritchie (91) on the desheathed vagus nerve fibers of rabbit, but the authors completely failed to recognize the significance of their observation. They consider it to be a purely pharmacological effect without any physiological significance (92) because physostigmine, at low concentrations, antagonizes this effect instead of potentiating it, as it does at the junction. This antagonistic effect has been fully explained by experiments of Hoskin and Rosenberg (93) in which they showed that these two structurally related positively charged compounds compete for the pathways by reacting with negatively charged components in the surrounding structure and that, therefore, in the presence of physostigmine, less ACh penetrates into the interior. No such competition is observed at the junction due to the absence of the external structure.

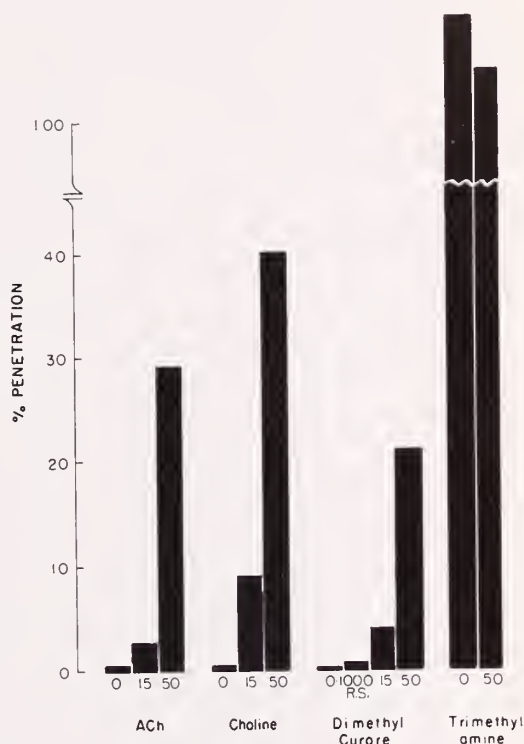
The demonstration of an action of ACh and curare and related compounds on axonal conducting membranes has also been achieved by chemical pretreatment by which the barriers have been reduced. Walsh and Deal (94) exposed desheathed bundles of frog sciatic nerve fibers to a detergent, cetyltrimethylammonium bromide. After the pretreatment and the removal of the detergent, curare, ACh and neostigmine reversibly blocked electrical activity.

Another chemical pretreatment for reducing the barriers was applied by Rosenberg and his associates. Snake venoms had long been assumed to increase the permeability of cell walls (95). Among a variety of snake venoms tested that of cottonmouth moccasin venom was found to be the most effective: after pretreatment of squid giant axons with a few micrograms of venom per ml for 15 to 20 minutes and after removal of the venom, ACh and curare rapidly and reversibly blocked axonal electrical activity (96). Phospholipase A appears essential for this action (97). Increased permeability is the factor responsible for rendering the axon sensitive to ACh and curare. This has been demonstrated by the following experiments. Squid axons were exposed to ACh and curare labeled with radioactive carbon; while radioactivity was hardly detectable in the extruded axoplasm of normal fibers, significant amounts of radioactivity were found in the axoplasm of pretreated axons. In contrast, very

high concentrations of another venom, that of the rattlesnake, which failed to render the axons sensitive to curare and ACh, did not increase the penetration of these compounds (Fig. 13), (98). In confirmation of previous observations a lipid soluble tertiary amine rapidly enters into the axoplasm even without pretreatment.

These developments have shown that the action of curare and ACh on the excitable mechanism of the membrane of conducting cells are not limited to the junction but may be obtained on the axonal membrane provided the sur-

FIG. 13. Penetration of radioactively (C^{14}) labeled ACh, choline, dimethylcurare and trimethylamine into the axoplasm of squid giant axon, with and without exposure to cottonmouth moccasin venom. The percentage indicates the radioactivity of the axoplasm compared to that in the outside fluid. The figures below the columns indicate the μg of venom/ml. In contrast to the moccasin venom that of the rattlesnake (R.S.), even in 1000 $\mu\text{g}/\text{ml}$, had no significant effect on the penetration of dimethylcurare. Trimethylamine readily penetrates with and without exposure to venom [according to data of P. Rosenberg and F. C. G. Hoskin (98)].



rounding structural barriers are sufficiently pervious to lipid soluble compounds or are reduced by proper chemical treatment.

The concentration of ACh and curare are higher than those required at the junctions. This is readily accounted for by the presence of remaining barriers surrounding the conducting membrane even under the best experimental conditions. The effects observed must be viewed in association with the huge amount of evidence in favor of the presence of the ACh system and its essential role in the permeability cycle of conducting membranes. It is pertinent that the effects postulated by theory, depolarization and increased permeability, have been demonstrated in several ways even if for quite obvious reasons the concentrations required are higher than those at the junction.

2. *Extracellular appearance of ACh.* The second line of evidence for the

neurohumoral transmitter hypothesis was based on the appearance of ACh in the perfusion fluid of junctions following the stimulation of nerve fibers. However, as was stressed time and again by Dale and his associates, ACh appears only when physostigmine is present in the perfusion fluid; not a trace is found in its absence. Since physostigmine is a potent and competitive inhibitor of ACh-esterase and since the ACh released under physiological conditions is rapidly hydrolyzed in milliseconds, block of this physiological mechanism must of necessity lead to leakage of ACh from the membrane of the junction and thus to its appearance in the perfusion fluid. In view of the many indications that the ACh system is structurally organized and its function associated with the membrane, one would expect that under physiological conditions not a trace would leak out of the cell. Thus, the leakage after gross interference with the physiological enzyme activity must be considered as an artifact. Loewi's "vagusstoff" appeared without added physostigmine; this experiment is, however, not reproducible. Ascher's claim (99), that the vagusstoff appears in the perfusion fluid only when the heart preparation (and, therefore, also the membranes) has severely deteriorated, seems to be correct. It may be mentioned that when axons are cut and stimulated, ACh also leaks from the cut surface where the barrier is now absent (100, 101).

The neurohumoral transmitter hypothesis postulates that the nerve terminal secretes ACh. In spite of the fact that this hypothesis has been so forcefully promoted for several decades, this crucial postulate has hardly been subjected to vigorous examination. In experiments by Dale and his associates (102) motor nerves of cat and dog muscles were sectioned; when after the degeneration of the nerve endings the muscles were stimulated directly, no ACh was detected in the perfusate. In contradiction to these findings McIntyre and his associates found ACh in the perfusion fluid after complete degeneration of nerve terminals when fibrillations of the muscle took place (103). In further extensive studies McIntyre found several factors which may account for the failure of the earlier observations to detect ACh in the perfusate (104).

Recently the results of McIntyre found a striking confirmation by the observations of Hayes and Riker (105). Ten days after section of the phrenic nerve of one hemidiaphragm of rats the release by the completely denervated muscle was identical to that by the innervated hemidiaphragm. Thus, most of the ACh in the perfusate is released from the postsynaptic membrane and not from the nerve terminal. Clearly, these data are incompatible with the idea of neurohumoral transmission.

3. Localization of the ACh system at the junction. The unified concept postulating a role of ACh in the permeability changes of synaptic and axonal membranes requires a localization of ACh-esterase in both pre- and postsynaptic membranes. Biochemical data obtained with a variety of muscle and nerve tissue preparation following sections of nerve fibers showed invariably a decrease of ACh-esterase activity in the synaptic region, roughly coinciding with the period of degeneration of the nerve terminals; then the re-

maintaining enzyme concentration did not change (24, 25, 106). The data suggest a high concentration of the enzyme in nerve terminals. A direct demonstration with histochemical techniques was difficult in view of the limitation of the resolving power of the light microscope. The recent results of Barnett (27), mentioned before, have demonstrated in a striking way that cholinesterase is localized in the two membranes of the junction, in the one covering the terminal and in the postsynaptic membrane. There was still some unexplained staining in the clefts that may be due to diffusion of products or to another type of esterase. Barnett's data are of crucial importance for the clarification of the precise role of ACh at the neuromuscular junction. They are the first direct demonstration of the localization in the membrane and show the presence of the enzyme in both membranes as postulated by the unified concept.

The functional significance of this enzyme on both sides of the junction has been demonstrated by the work of many investigators. In 1940, Masland and Wigton (107) found that neostigmine applied to the neuromuscular junction produces rapid discharges in the ventral motor roots in addition to its action on the muscle. Curare abolishes both effects. The authors fully recognized that their data are incompatible with the assumption of an action of ACh being limited to the postsynaptic membrane. In recent years the results were confirmed and greatly extended by Riker and his associates (108), and others. It is today well established that curare, ACh, neostigmine and related compounds act on the membrane of the nerve terminal in the same way as on the postsynaptic membrane [for a recent summary see Werner and Kuperman (109)]. Obviously, these compounds act on comparable macromolecules in both membranes associated with the permeability changes responsible for electrical activity. The system is not only present but functionally essential for the excitable mechanism. Curare blocks the nerve terminal in even lower concentrations than the postsynaptic membrane.

The role of ACh in synaptic transmission may then be pictured in the same way as in axonal conduction: when the currents reach the nerve terminal, ACh is released in the presynaptic membrane and acts there on the receptor; the membrane is depolarized, Na ions enter, K ions move out into the synaptic gap. These ion movements, or the resulting currents, will cross the gap and release ACh in the postsynaptic membrane which then acts on the receptor and generates the postsynaptic potential. This leads to an excitation of the effector cell, nerve or muscle. Injection of K ions into the neuromuscular junction is known to produce a twitch, indicating that these ions apparently are capable of releasing ACh in the membrane from its bound form; a direct action of K ions would be hard to reconcile with the type of transitory effect observed.

F. CHEMICAL REACTIONS AND THEIR RELATION TO STRUCTURE, ORGANIZATION AND FUNCTION

Like all biological phenomena, axonal conduction and synaptic transmission are highly complex processes involving an interplay of a variety of chemical reactions and physical changes. Strong evidence has accumulated in support

of the view that the ACh system is essential for controlling the permeability changes of the two synaptic membranes and in those of nerve and muscle fibers. The idea of the role of ACh at synaptic junctions being fundamentally different from that in the conducting membrane has become untenable. The system is localized and functional in the pre- and postsynaptic membranes. The assumption of a secretion of ACh from the nerve terminal and acting as a neurohumoral transmitter has been contradicted.

The fundamental similarity of the role of ACh in the synaptic and conducting membranes will not appear surprising to the biochemist, accustomed to think in terms of the biochemical unity of life. Nature has shown very little imagination as far as the chemical and physicochemical forces acting in cellular functions are concerned. The energy released by the hydrolysis of ATP is used for a wide variety of biosynthetic reactions; it is used in combination with actin and myosin for motility throughout the animal kingdom. The citric acid cycle is widely used in low and primitive as well as in highly developed and differentiated cells. A great number of examples of this kind could be quoted. They emphasize how rare and relatively small the modifications of chemical forces are which have taken place in the course of evolution.

Nature has, however, developed a nearly unlimited number of variations of structure and organization whereby the effects of special chemical reactions may be greatly modified and adjusted to the functional requirements of the cell. Much insight has been obtained during the last decade about the structure and organization in relation to function on cellular, subcellular and molecular levels, a development greatly stimulated by the extraordinary advances of instrumentation and methods.

In the classical era of enzymology, some fifteen to twenty years ago, the chief aim of enzyme chemists was the preparation of an enzyme in a pure or highly purified form and to study its specificity, its kinetics, and its association with other chemical reactions. In the last decade, biochemists have become increasingly interested in the secondary and tertiary structure of proteins, nucleic acids and other macromolecules, in the active sites of enzymes and their conformational changes during the active state. Structure and organization of macromolecules in relation to function has become one of the most actively studied topics in a field widely referred to as molecular biology.

Many enzyme catalyzed reactions are structurally organized within the cell. The fascinating advances in the field of genetics and the role of nucleic acids in protein synthesis are providing much insight into the role of organization of cellular mechanism. An illuminating example of structural organization of enzymes is the oxidative system as has become apparent mainly from the work of David E. Green and his associates: the electron transfer system is a mosaic of many enzymes organized in the cristae of mitochondriae and linked structurally and functionally in a precise pattern (110).

The understanding of structure and organization of chemical systems within subcellular units may help to bridge the gap between test tube reactions and cellular function. This is well illustrated by the striking advances

achieved in the understanding of the elementary process of muscular contraction: the successful combination of electron microscopy, optical methods and biochemical studies has revealed the sliding mechanism of the actin and myosin fibrils (54). On the other hand, it appears likely that the many differences between the different types of contractile fibers are not due to a basic difference of interaction between ATP, actin and myosin, but to differences of structure and organization.

In the case of the plasma membrane of conducting cells information about structural organization is still quite restricted, partly due to the small dimensions of the membrane for which the resolving power of present electron microscopes may not yet be fully adequate. But it is well known that the gross structure and organization of axons show great differences of diameters, which may vary from 1 to 1000 μ , of relationships of the inner to the total diameter, of presence or absence of Ranvier nodes, etc. (Fig. 14), (111). Correspondingly, physical parameters, such as heat production, speed of conduction, and others, also vary considerably. The speed of conduction, for instance, may

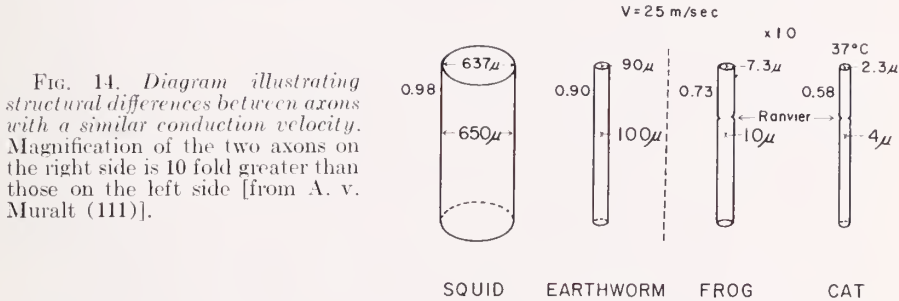


FIG. 14. Diagram illustrating structural differences between axons with a similar conduction velocity. Magnification of the two axons on the right side is 10 fold greater than those on the left side [from A. v. Muralt (111)].

vary from 0.1 to 100 m per second. We have seen that the concentrations of ACh-esterase and of choline acetylase in different axons vary over a wide range. Nobody has suggested a difference of the fundamental mechanism underlying electrical events in axonal conduction on the basis of differences of these parameters.

The structural variations at the junction between nerve and nerve and nerve and muscle (telodendria, dendrites, etc.) are of a completely different dimension and nearly infinite in number. The tremendous increase in surface area by the endarborization of the nerve terminal and by the deep folds of the postsynaptic membrane surrounding the terminals at the neuromuscular junction, or by some of the dendritic formations, for instance, must have a big influence on the various physical parameters, even if the underlying molecular events in the membranes are similar. We cannot decide, at present, to what extent the underlying chemical reactions are similar except for the role of the ACh system since this is the only one intensively investigated and where a large amount of information has accumulated; but even in this case, as pointed out before, remain many gaps as to the precise mechanism. It is obvious, however, that the extensive variations of shape, form and structure of the mem-

branes must have a very great impact on the functional effects resulting from a chemical reaction such as that postulated for ACh: the effect of a change of ionic permeability in a membrane having the shape of a simple cylinder such as the axonal membrane, may differ greatly from that of the same chemical reaction taking place in a membrane with a highly complex shape. It is, therefore, not surprising that the physical parameters observed during activity show not only similarities but also various modifications. But this does not entitle us, as has been done so frequently in the past, to postulate a basically different mechanism underlying the permeability changes in the membranes which must take place during activity, or to attribute to a chemical reaction two different functions.

Whether the great differences in structure at junctions are entirely responsible for the modifications of the electrical characteristics, for instance the inability of the postsynaptic membrane to propagate the impulse and to reverse the charge observed in the axonal membrane (the so-called "overshoot") or whether there are additional chemical forces contributing to this difference, is at present a moot question since no information is available. In a membrane of 100 Å thickness there is ample space for a variety of chemical reactions. If the effect of the postulated conformational change of the receptor protein is assumed to be a shift of charge, such a reaction may not be specific and may require additional chemical forces entering into the picture in several ways. Additional regulatory systems may be present in some of these membranes and absent in others.

The classical methods of physiology and pharmacology are still of great importance for obtaining valuable information about many aspects of the function of the nervous system. But they are not adequate to provide answers to the many specific problems which must be solved if we want to understand the chemical and molecular processes in the conducting membrane during activity. The analysis of the molecular forces acting in the membrane, of the macromolecules, phospholipids, polyelectrolytes, etc., the effects of structure and organization on these forces, all these studies must in the future be intensified on the lines frequently referred to in this paper. They offer the best promise to obtain eventually a comprehensive picture of the mechanism of the generation and propagation of bioelectric currents, nature's way of carrying messages.

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RADIOLOGICAL NOTES

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CASE NO. 244

A 63 year old female was admitted to the hospital because of shortness of breath. The patient had been under an emotional strain for some time, details of which were not well documented. On the day of admission she developed



Case 244, Fig. 1. Anteroposterior view of the right knee shows calcifications uniformly distributed in the articular cartilages. The bones are normal.

progressive shortness of breath and tightness in the chest without frank chest pain. Past history revealed no serious medical illnesses. She had complained of pain in both knees from time to time, and recent pain in the left shoulder was attributed to bursitis. No history of trauma was elicited.

From the Department of Radiology, The Mount Sinai Hospital, New York, N.Y.

On admission, physical examination revealed a few fine dry rales at both bases but otherwise there were no positive findings. Temperature was 101°. ECG revealed no abnormality. Initial laboratory studies revealed hemoglobin 16 Gm, hematocrit 45, white blood count 15,000 with moderate left shift and



Case 244, Fig. 2. Anteroposterior view of the left shoulder shows calcifications in the articular cartilage paralleling the humeral head. The bones are normal. No para-articular or soft tissue calcifications are present.

urinalysis entirely normal. Other studies included blood urea nitrogen 17.5 mg%, uric acid 10 mg% and 12.8 mg%, calcium 5.5 mEq/L, alkaline phosphatase 4.5 Bodansky units, latex fixation negative and C-reactive protein 3 plus. On repeat blood count five days after admission the hemoglobin was 14 Gm and white blood count 9,000 with normal differential.

Radiographic examination of the chest showed a few densities at both bases suggesting multiple foci of bronchopneumonia or possibly pulmonary emboliza-

tion. Radiographic examination of the knees and left shoulder were performed followed by examination of the remainder of the extremities and pelvis. (A total survey of the bones was not performed.) All of the visualized joints revealed thin linear and mottled calcifications in the articular cartilages characteristic of chondrocalcinosis (Figs. 1, 2 and 3).

The patient became afebrile on antibiotic therapy. Repeat chest x-ray revealed a changing picture of the basilar densities tending to support a diagnosis of pulmonary embolization. The patient's mental status was poor during



Case 244, Fig. 3. Anteroposterior view of the pelvis shows calcifications in the cartilaginous disc at the pubic symphysis.

hospitalization and deteriorated into a frank paranoid reaction which necessitated transfer to another institution. No follow-up information is available.

DISCUSSION

Chondrocalcinosis is a chronic disease of joints characterized radiographically by calcification in and around joints. Although only a limited number of case reports have appeared in the literature, the entity is not rare and is now being recognized with more frequency. Clinically, patients experience intermittent attacks of joint pain often associated with synovial reaction. Because of the similarity to gout in this regard, the term "pseudogout" has been used (1); this terminology is not helpful and should be abandoned. The dis-

ease is of unknown etiology, has no sex predilection and appears to be hereditary in many cases.

The definitive laboratory finding is the presence of calcium pyrophosphate crystals in synovial fluid. The appearance of the crystals allows a presumptive diagnosis on direct smear, but this should be confirmed with x-ray diffraction studies. Serum uric acid levels are sometimes elevated as in the case reported here (2, 3), but other routine laboratory tests are within normal limits.

The characteristic radiographic finding is generalized calcification of articular cartilage. The calcium is usually deposited in an orderly fashion in both fibrous and hyaline cartilage (4). Para-articular calcifications do occur (3) and hypertrophic and degenerative joint changes often supervene as well. Eventually articular cartilage is destroyed, the calcification becomes disorganized and less obvious, and the radiographic picture becomes mixed and nonspecific (4). In the differential diagnosis hyperparathyroidism should be excluded by appropriate laboratory studies, since articular calcifications may occur in hyperparathyroidism entirely similar to those seen in chondrocalcinosis.

Case Report: CHONDROCALCINOSIS

ACKNOWLEDGMENT

The editors wish to thank Dr. Paul Barr, Good Samaritan Hospital, Suffern, N. Y., for permission to use this case.

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CASE NO. 245

A 72 year old woman noted a large lump in the central portion of the left breast. It did not change in size over a one-month period of self-observation. There had been no trauma, the breast was not painful, and there was no drainage from the nipple. There was no past history of breast disease and general health had been good except for moderate hypertension. Physical examination confirmed a peach-sized mass in the central portion of the left breast. The mass was somewhat irregular in outline, firm but not rocky hard, and non-tender. There was no sign of skin involvement or deep fixation. No other mass was palpable in either breast and there were no enlarged lymph nodes. The remainder of the physical examination was not contributory.

Radiographic examination of the breasts revealed a 7 cm ovoid mass in the upper central portion of the left breast (Figs. 1 and 2). Although the margins

were not grossly irregular, they were somewhat ill-defined and not sharp. There was no infiltration into the surrounding tissues. Skin and nipple shadows were normal. No abnormal calcifications were present. There were no other



Case 245, Fig. 1. Lateral views of both breasts show a 7 cm ovoid lesion in the upper portion of the left breast. The margins are ill-defined. There is no infiltration into the surrounding tissues. No abnormal calcifications are present. There is no corresponding mass in the right breast. The breasts are otherwise atrophic.

masses. In the differential diagnosis the radiologist excluded a simple benign lesion and recognized the poor margination as an indication of a malignant neoplasm or an acute inflammatory process. The lack of surrounding infiltration excluded the usual scirrhous carcinoma and pointed to a bulky, cellular non-infiltrating carcinoma, a less common variety. An outside possibility con-

sidered was a cystosarcoma phylloides. The history did not suggest an acute inflammatory process. Routine laboratory studies and radiographic examination of the chest, urinary tract and entire gastrointestinal tract were normal.

At surgery, a biopsy with frozen section was followed by simple mastectomy. The pathologist reported a circumscribed but nonencapsulated lesion histo-



Case 245, Fig. 2. Cranio-caudad views of both breasts again demonstrate the large lesion in the left breast.

logically typical of lymphocytic lymphosarcoma. Postoperatively the patient was referred for radiation therapy to the lymph node bearing areas of the left breast.

DISCUSSION

Standard reference texts of general pathology (1), surgical pathology (2) and oncology (3) describe the occasional occurrence of lymphosarcoma within

the breast. The lesion may be localized or part of a generalized disease. When localized, surgery is recommended as the treatment of choice (4) but there is insufficient material in the literature for an accurate statistical analysis.

The radiographic appearance of lymphosarcoma in the breast is not well established. No reference to this disease is made by Ingleby and Gershon-Cohen in their book (5). In the case presented, the radiographic features mirror the gross pathology, *i.e.*, a circumscribed but nonencapsulated lesion. Figures 1 and 2 demonstrate the ill-defined margins of the lesion which exclude the radiographic diagnosis of a simple benign lesion such as a cyst or fibroadenoma. The absence of infiltration indicates a lesion growing by expansion. The asymmetry of the process and the atrophic nature of the breasts excludes a large zone of fibrocystic hyperplasia. A localized inflammatory process might present this picture, but the skin and adjacent breast tissues give no evidence of inflammation; further, the history and physical findings speak against the diagnosis as well. Although the most likely radiographic diagnosis is a bulky, cellular adenocarcinoma, the case presented emphasizes that lymphosarcoma may produce a similar picture and must be considered in the differential diagnosis despite its rarity.

Case Report: PRIMARY LYMPHOSARCOMA OF THE BREAST

ACKNOWLEDGMENT

The editors wish to thank Dr. Michael J. Cavanagh, Good Samaritan Hospital, Suffern, N. Y., for permission to use this case.

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POST BULBAR DUODENAL DIVERTICULA: A REPORT AND DISCUSSION OF FOUR CASES

Diverticula of the first portion of the duodenum are rare and usually are situated in the post bulbar region. Up to 1939, Edwards was unable to find a single proven case in the literature (1). It is now believed that diverticula of the first portion of the duodenum represent less than 3 per cent of all duodenal diverticula. Many of the outpouchings described in the region of the bulb represent pseudodiverticula associated with ulcers. On the other hand, more than 75 per cent of duodenal diverticula are located within the second portion, within 3 cm of the ampulla of Vater.

Duodenal diverticula are usually of the false type, lacking a muscular coat (2). Although their etiology is not clear, they are probably formed by a muco-

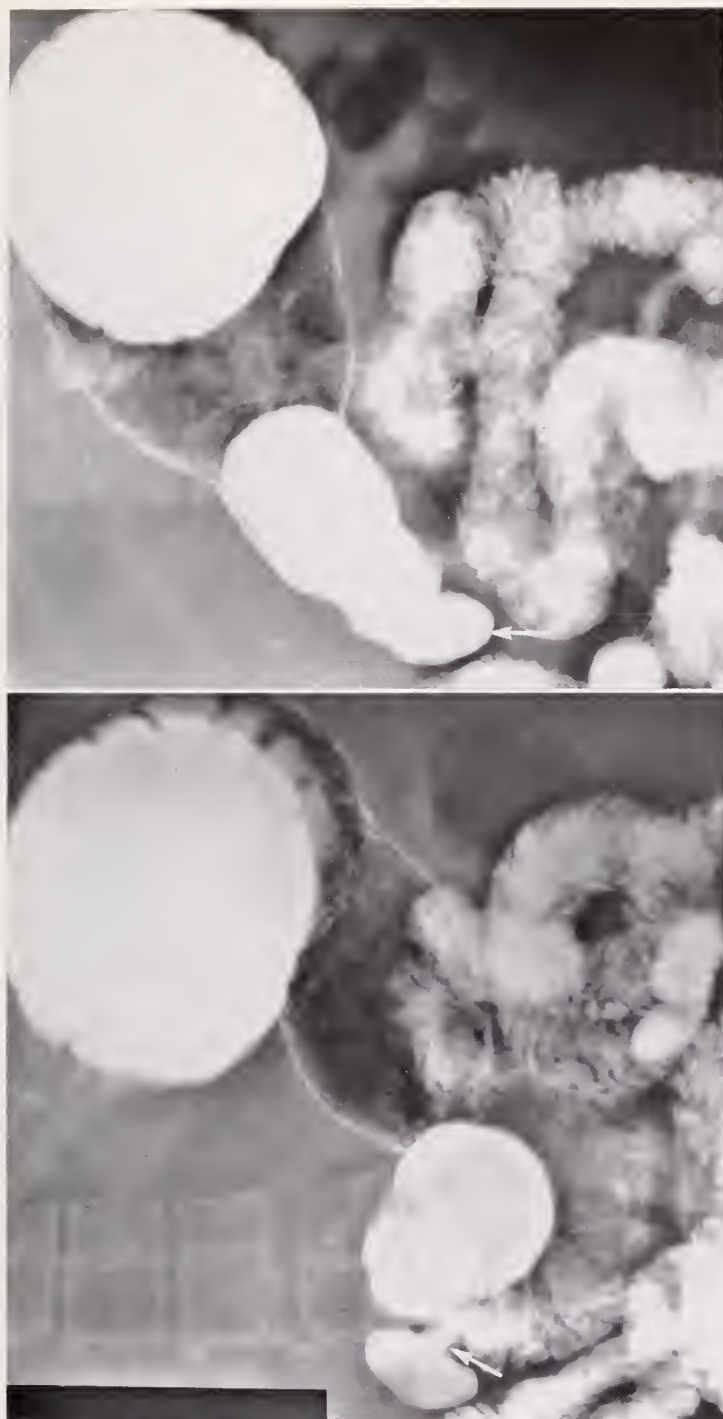


Fig. 1A. Right anterior oblique roentgenogram during a barium meal examination reveals a 2 x 3.5 cm diverticulum with a narrow neck (arrow) arising from the lesser curvature aspect of the post apical region of the duodenum. The bulb is not deformed. The folds of the second portion of the duodenum are normal.

Fig. 1B. Anteroposterior view during the course of the same examination reveals the diverticulum (arrow) which appears to be superimposed upon the lateral aspect of the second portion of the duodenum. Without the proper oblique projection (Fig. 1A), its true anatomical position could not be appreciated.

sal and submucosal evagination through a weakened portion of the muscular wall (3). In the first segment of the duodenum, diverticula usually present as outpouchings, arising from the lateral or lesser curvature aspect of the superior "knee" of the duodenum (Figs. 1, 2, 3). Only rarely are they seen as a projection along the greater curvature of the first part of the duodenum (4). They are almost never seen to arise from the body of the duodenal bulb



Fig. 2. A 1 x 4 cm diverticulum extends laterally from the post apical portion of the duodenal bulb (arrow). It has a narrow neck and contains a few lucent defects which probably represent retained material. An air fluid level is noted in the diverticulum and in the bulb. The latter is not deformed.

proper. The diverticula vary considerably in size, but are usually smaller than the duodenal bulb itself. They usually assume a mushroom-like configuration with a narrow neck (Figs. 1, 2). Fluoroscopically, they can be seen to fill and empty with striking changes in size and configuration. Mucosal folds, which are continuous with those of the main portion of the duodenum, can frequently be traced into the neck of the diverticulum (Fig. 4). On occasion, retained food and secretions can be delineated within the diverticulum during the initial phases of the roentgen examination (Fig. 3).



Fig. 3A. Lateral roentgenogram of the duodenal region reveals a broad neck diverticulum measuring 2×5 cm and arising from the lesser curvature aspect of the post apical segment of the duodenum (arrow). The folds of the adjoining of the duodenum are well seen and appear normal. The bulb is not deformed.

Fig. 3B. A right anterior oblique view during an earlier phase of the same examination shows the diverticulum containing a large, smooth filling defect (between arrows) which represents a retained food particle.

Post bulbar diverticula are usually an incidental finding during the course of an upper gastrointestinal examination. The importance of their recognition is thus mainly in their differentiation from ulcerations within the duodenal bulb and post bulbar regions (4). As noted previously, post bulbar diverticula change in size and configuration, contain normal mucosal folds within their necks that can be traced into the adjacent duodenum, and usually project upwards and laterally along the contour of the superior "knee" of the duodenum. The duodenal bulb itself is not deformed. Post bulbar ulcers, on the other hand, typically present as an amorphous barium patch which does not

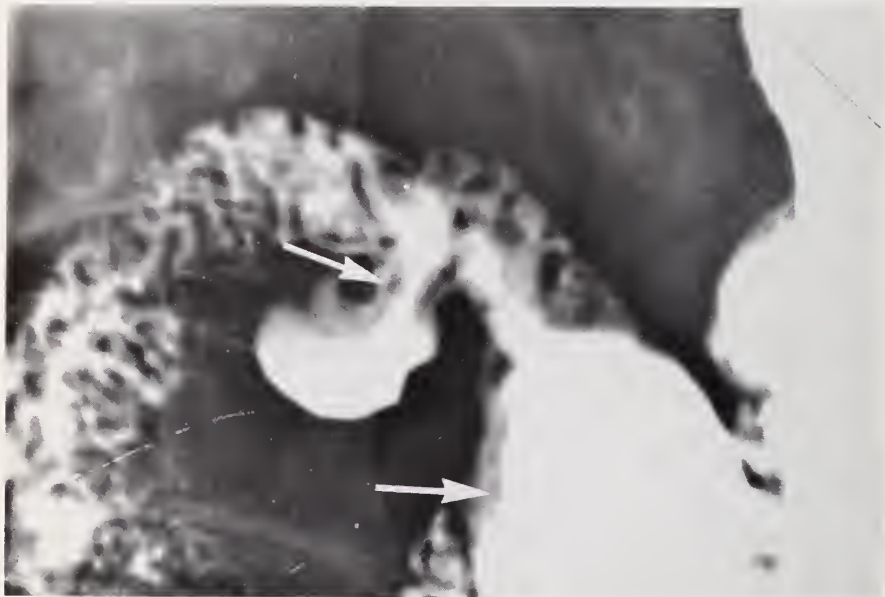


Fig. 4. A rounded diverticulum with a narrow neck (upper arrow) is noted to arise from the inferior-greater curvature-aspect of the post bulbar region. The folds can readily be traced from the duodenum through the neck into the diverticulum. The duodenal bulb, whose distal half can be seen on this spot film (lower arrow), is not deformed.

change in size or configuration during the examination. The folds around the crater are thickened and distorted and there is often considerable irritability of the adjacent segments of the duodenum. The apex of the duodenal bulb is usually narrowed and deformed (Fig. 5).

Ordinary pseudodiverticula of the duodenal bulb are usually easily recognizable when proper pressure spot films are available and a constant deformity of the bulb, with or without an associated crater, is demonstrated. Often, pseudodiverticula are located in the proximal portion of the bulb and can be seen along either or both curvatures. These pseudodiverticula can be noted to change in size and shape, but unlike post bulbar diverticula they do not contain mucosal folds.



Fig. 5A. There is an amorphous collection of barium (arrow) in the post bulbar region of the duodenum. The mucosal folds around the crater are thickened and distorted and there is a narrowing of the apex of the duodenal bulb.



Fig. 5B. Pressure spot film again reveals the post bulbar crater (arrow) with the surrounding mucosal thickening and distortion, as well as the abnormal filling of the adjacent portion of the descending duodenum.

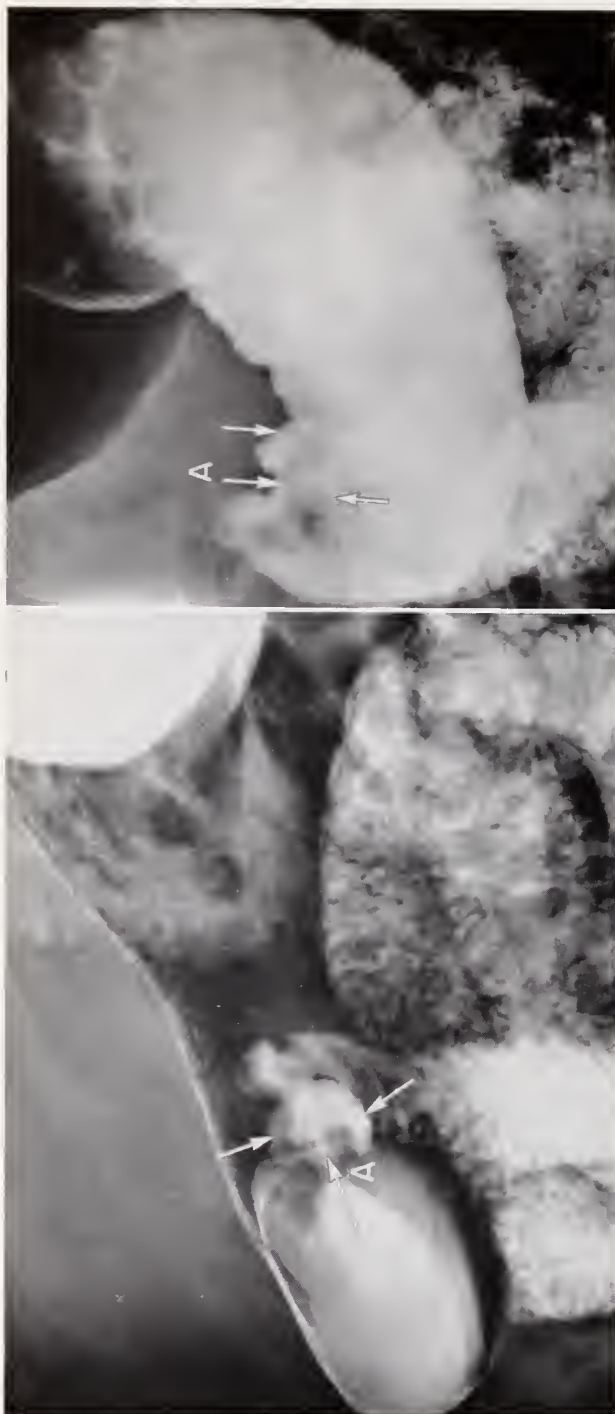


Fig. 6A. A rounded collection of barium is noted in the region of the duodenal bulb (between arrows) with a narrow proximal contour (arrow A). The folds of the post bulbar region are thickened (seen through the gas in the body of the stomach).

Fig. 6B. The previously described rounded barium collection (between arrows) has remained unchanged in size and configuration with the same proximal narrowing (arrow A). This represents a giant benign ulcer replacing the entire duodenal bulb and penetrating posteriorly into the bed of the pancreas.

Giant benign ulcers of the duodenal bulb are rare and occasionally can mimic post bulbar diverticula. However, when the ulcer replaces most or all of the bulb, the resultant barium containing structure is noted to be unchanging in size and configuration and the remaining portion of the bulb is markedly deformed (5) (Fig. 6). The duodenal folds in the adjacent portions are effaced and distorted and the barium assumes an amorphous character.

SUMMARY

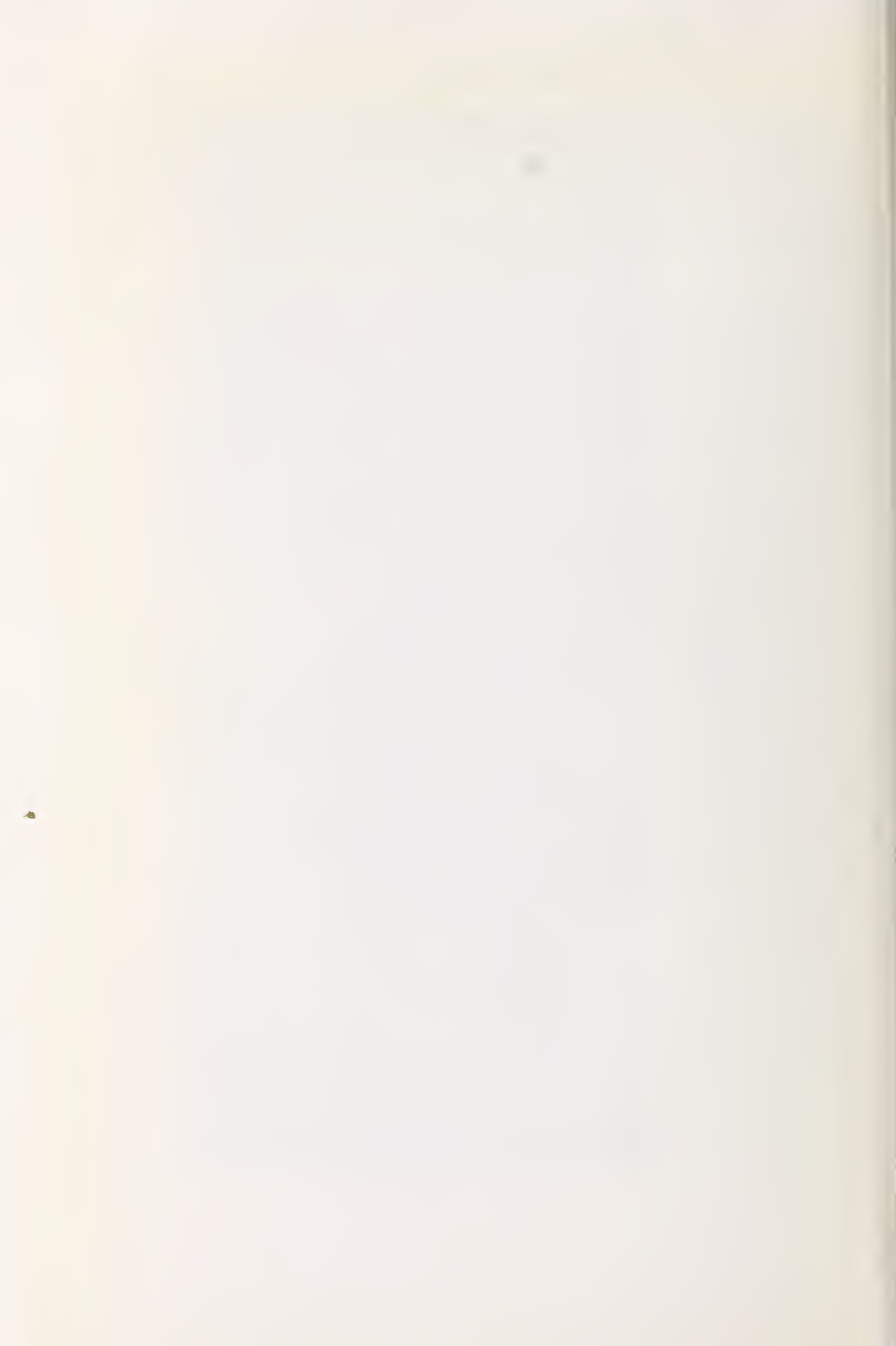
The characteristics of post bulbar diverticula are described and their differentiation from post bulbar ulcers, giant benign duodenal ulcers, and pseudo-diverticula of the bulb is discussed. Four cases are presented.

ACKNOWLEDGMENT

Case No. 6 is presented through the courtesy of Dr. Howard L. Moscovitz.

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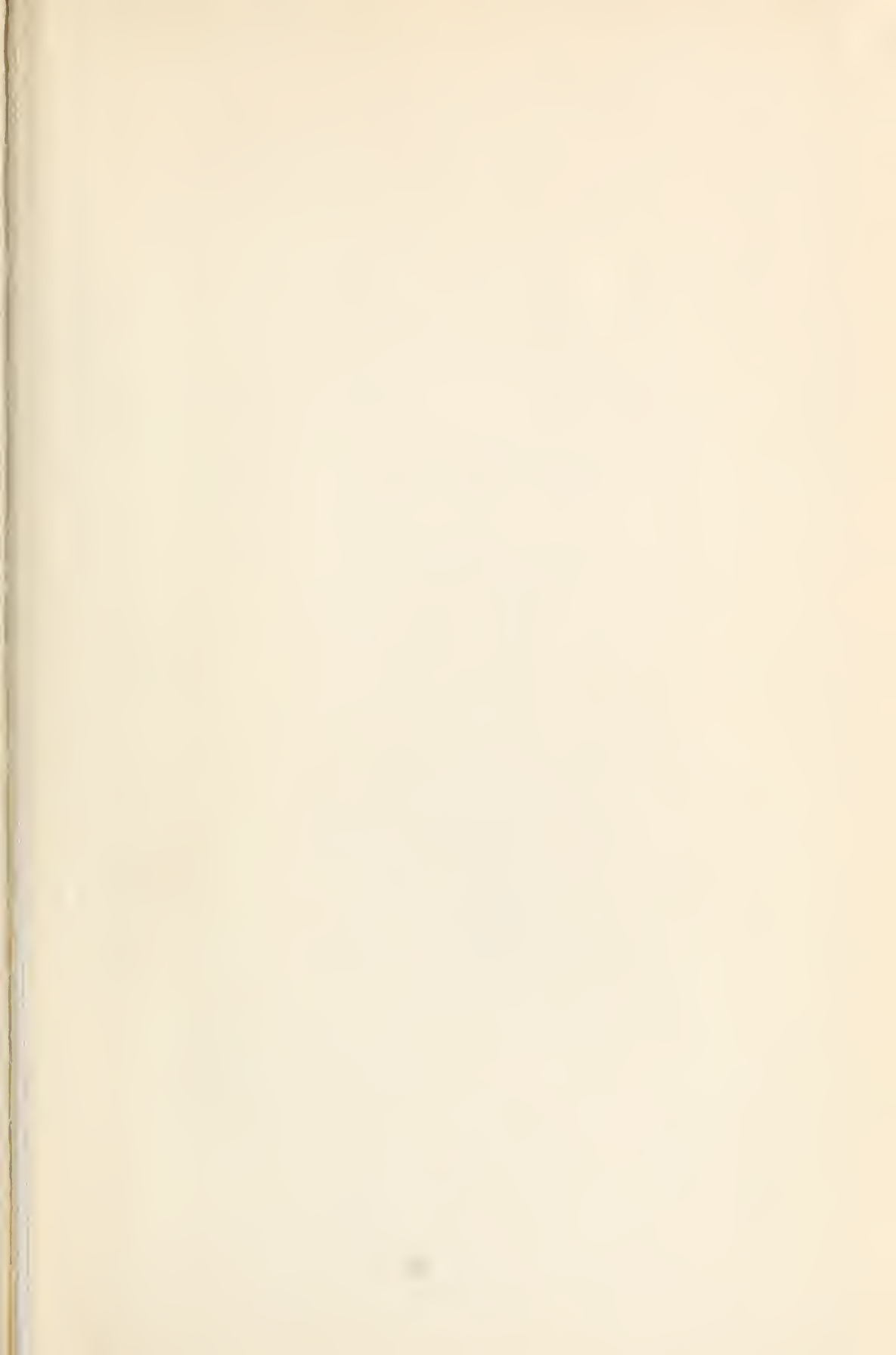
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